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P A R T I C I P A N T S

Gary S. Eglinton, M.D., Chairperson
Elisa D. Harvey, D.V.M., Ph.D., Executive Secretary

Voting Members

Jorge Blanco, M.D.
Donald Chatman, M.D.
Thomas Downs, Ph.D.
Karen Maples, M.D.
Michael Neumann, M.D., Ph.D.
Johanna Perlmutter, M.D.
Gerald Shirk, M.D.

Industry Representative

Cindy Domecus, R.A.C.

Consumer Representative

Diony Young

FDA

Colin Pollard, Chief, Obstetrics and Gynecology
Devices Branch, Center for Devices and Radiological Health

Yunk Pak
John Murray
Brian Harvey, M.D., Ph.D.
Richard Kotz

C O N T E N T S

P R O C E E D I N G S

CHAIRMAN EGLINTON: Okay. Let's go ahead and come to order, please.

We have the sign-in sheets out front. Please, everyone, sign in. We have a large and rather robust-appearing audience today. Make sure that if there are any comments that you wait until you're acknowledged from the chair and then come to the podium, identify yourself fully and who paid your bills to get here, stay here, and talk and so forth.

Now we'd like to have the panel members introduce themselves. We'll start with Dr. Blanco, opposite me, and then move to his left.

DR. BLANCO: I'm Jorge Blanco. I'm the medical director of Sacred Heart Women's Hospital in Pensacola, Florida.

DR. E. HARVEY: Dr. Chatman will be here in a minute, and we'll introduce him then.

DR. SHIRK: I'm Dr. Jerry Shirk. I'm a clinical associate professor at the University of Iowa and have basically done a lot of work with hysteroscopy.

DR. DOWNS: I'm Tom Downs, professor of biometry, University of Texas School of Public Health.

MS. DOMECUS: Cindy Domecus, Senior Vice President

Clinical Research, Regulatory Affairs and Quality Assurance at Conceptus, and I'm the industry rep on the panel.

DR. YIN: I'm Dr. Yin. I'm with FDA, Director, Division of Abdominal, Reproductive, ENT, and Radiological Devices.

MS. YOUNG: I'm Diony Young from Geneseo, New York. I'm editor of the journal Birth, and I'm the consumer member of the panel.

DR. PERLMUTTER: I'm Johanna Perlmutter. I'm an obstetrician-gynecologist at Beth Israel Hospital in Boston.

DR. NEUMANN: I'm Mike Neumann. I'm from the Departments of Obstetrics and Gynecology and Biomedical Engineering at Case Western Reserve University in Cleveland, Ohio.

DR. MAPLES: I'm Karen Maples. I'm an OB-GYN practicing at Kaiser Foundation Hospital, Bellflower, California.

CHAIRMAN EGLINTON: I'm Gary Eglinton, Director of Maternal-Fetal Medicine, Georgetown University.

DR. E. HARVEY: I'm Elisa Harvey, a member of the Obstetrics and Gynecology Devices Branch and the Executive Secretary for this panel.

CHAIRMAN EGLINTON: The FDA press contact for the day's meeting is Sharon Snyder.

Okay. We do have a full agenda. If you have comments to offer, please keep them brief, concise, and to the point. I understand we do have a referee within the presenting group. We'll have no outbursts, please. Just be recognized and come to the podium.

Elisa?

DR. E. HARVEY: A little bit of housekeeping first. The panel members should have in front of them the lunch menu, so if they could fill that out and pass that along to the corner, then we can collect those and give them to the person who will have your lunch ready for you at the break.

I mentioned that Dr. Chatman will introduce himself when he gets here. He'll be here shortly, and he's the newest member of our panel.

I would like to read a couple of documents into the record. The first is the appointment to temporary voting status.

"Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, and amended April 20, 1995, I appoint the following people as voting members of the Obstetrics and Gynecology Devices Panel for the duration of this panel meeting on October 6 and 7, 1997: Dr. Donald Chatman, Dr.

Thomas Downs, Dr. Washington Hill, who will participate tomorrow, Dr. Karen Maples, Dr. Michael Neumann, Dr. Johanna Perlmutter, and Dr. Gerald Shirk.

"For the record, these people are special government employees and are consultants to this panel. They have undergone the customary conflict-of-interest review, and they have reviewed the material to be considered at this meeting."

It is signed by our Center Director, Dr. Bruce Burlington.

The next statement I would like to read into the record is the conflict-of-interest statement.

The following announcement addresses conflict-of-interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict-of-interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the

potential conflict of interest involved, is in the best interest of the government.

Waivers have been granted to Drs. Donald Chatman and Johanna Perlmutter for their interest in firms at issue that could potentially be affected by the committee's deliberations. The waivers permit these individuals to participate in all matters before the panel. Copies of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration certain matters regarding Dr. Johanna Perlmutter.

Dr. Perlmutter reported that colleagues within her department are investigators for this subject device. However, she does not have any managerial responsibilities over the colleagues, nor is she involved in the study. Therefore, the agency has determined that she may participate fully in today's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants should excuse themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in

the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

I'd like to also note for the audience that transcripts or videos will be available. The information is on the desks out in the area out front.

Finally, any presenters to the panel who have not already done so should provide FDA with a hard copy of their remarks, including any overheads. Yung Pak will collect those from you at the podium. Yung, could you stand for everyone?

To the panel, I'd like to note that there are a couple of additional enclosures that were stuck into your day-of folder at the last minute. You have a table of contents that should explain everything that's in there.

CHAIRMAN EGLINTON: Mr. Colin Pollard will now give us a brief overview of the purpose of this panel meeting.

MR. POLLARD: Thank you, Dr. Eglinton. Good morning, members of the panel, distinguished audience.

This morning before we get under way, I'd like to just briefly give you FDA's charge today and go over a little bit of background material. I'd first like to

welcome back Dr. Downs, Dr. Perlmutter, and Dr. Maples to the panel for this particular day--we appreciate you coming--and as well as welcoming Dr. Chatman for the first time.

Today we have a premarket approval application for a product called ThermaChoice. It's a uterine balloon therapy system sponsored by Gynecare, and I would like to just go over a little bit about what this PMA is about and bring you to the specific charge regarding the premarket approval application.

The uterine balloon therapy system is designed to treat abnormal uterine bleeding, and as we all know, it's very important in dealing with this to clearly define what we mean by abnormal uterine bleeding--that definition sometimes can get a little complex--and to have appropriate patient workup beginning with medical management and then turning, if necessary, to surgical management. In your folders, you will see a couple of ACOG advisories in this regard. You'll that this becomes important as we talk specifically about the clinical study to support such a device.

The uterine balloon therapy is one of a new kind of device for endometrial ablation, and specifically, there are new design features for this kind of system. The terminology you may hear either today or elsewhere in your

dealings is terms like "global" and "auto-ablative." This is a system that is a lot different from the kinds of devices used today to do endometrial ablation, and specifically, it includes an intrauterine latex balloon catheter and a heating element and achieves endometrial ablation through thermal means. Its clinical implications go to a simpler, shorter procedure, and in particular, it essentially eliminates the risk of fluid intravasation and the consequent clinical sequelae.

The endometrial ablation systems used today go back to the early, mid-eighties, first with the hysteroscopic endometrial ablation system. The Nd:YAG laser fiber was described by Goldrath in 1981, and FDA cleared the first 510(k) for this kind of product in 1986. This device is used under hysteroscopic observation where the surgeon meticulously goes over the entire endometrial surface. A modified resection/rollerball system was described by Tucherney (?) in 1986, and the first 510(k) for this kind of product was cleared in 1989.

These new kinds of global auto-ablative systems essentially are dealing with the same indication for use, namely, endometrial ablation for women with abnormal uterine bleeding, but because of the design characteristics of these devices, they raise new types of safety and effectiveness

questions. And what this means from a regulatory point of view is that this product type switches from the 510(k) track to the PMA track.

What does this mean? Well, first of all, clinical investigations are needed to support the premarket approval application, and as you know, FDA tries to work with manufacturers starting as early as possible, beginning usually with what we call pre-investigational device exemption applications where we look at preliminary clinical trials.

In parallel with that, we also convened our panel back in October of 1995 to essentially look generally at this area and generally at the kinds of clinical studies that would be needed to show safety and effectiveness for this product, and in particular, we looked at draft IDE guidance, and this guidance would be intended to spell out the requirements for both initial studies for safety as well as subsequent studies that would essentially establish the safety and effectiveness of the device for a premarket approval application.

At this point, I would like to just do a couple of acknowledgments. First of all, I'd like to Donna-Bea Tillman. Dr. Tillman, who is a biomedical engineer in our Office of Device Evaluation and now is an acting branch

chief in a different branch, for the three years she was with the branch this was one of her primary work objectives in working on the guidance for this kind of product and the review criteria. I'd also like to acknowledge Dr. Barbara Levy and Dr. Mike Diamond from the panel who are not with us today. Together with Dr. Tillman they essentially wrote the guidance document that we're working with today that the panel looked at in October and was finalized shortly after that. And, finally, I'd like to acknowledge Dr. Shirk, Jerry Shirk, who came to our October meeting as a guest speaker, is now a consultant to the panel, and was engaged on this PMA as well.

I'd like to turn to that guidance document for a moment. You have a copy of it in your folder. It was finalized a few months after our panel meeting in October '95, and in particular, it deals with the issue of the device design itself, in particular the safety profile for that kind of device, at the initial safety studies where we studied pre-hysterectomy patients to look at the thermal effect of these devices, the pilot effectiveness study, and, finally, the pivotal safety and effectiveness study that would support a PMA.

In that pivotal safety and effectiveness study, the guidance document points to the importance of carefully

defining the primary outcome measure, the inclusion and exclusion criteria, and methodological details, including statistical power, the study size, pre-treatment, if any, and the length of follow-up. In particular on the length of follow-up, the panel had recommended a one-year follow-up in a premarket situation followed by a two-year follow-up in the postmarket setup. And, lastly, the guidance document speaks to the protection of human subjects, including informed consent and institutional review board approval.

Today's PMA requires that the panel consider-- sorry. A couple of other points about the PMA today is this is a first-of-a-kind device. In particular, we have never reviewed a thermal endometrial ablation system, especially one that is sort of a global auto-ablative system. I'd like to point out that the overall study plan seems to conform to the guidance document that the panel and FDA drew up. And FDA put together a PMA review team that focused on both hardware components of this device, the software, which is a key element to making the system work properly, and the appropriate clinical and biostatistical components as well.

The panel recommendation, as you know--and Elisa will go over with you later--needs to take the form of either an approval, an approval with conditions, or not approvable.

PMAs, as you know, need to be based on valid scientific evidence, in particular, well-controlled studies, although the panel is also able to look at partially controlled studies, studies in objective trials without matched controls, as well as case histories and reports of significant human history. And in considering a PMA, the panel needs to consider both the safety and the effectiveness of the device.

The regulation for PMAs: Defined safety is when the probable benefits outweigh the probable risks, when the device is used according to its labeling. And it defines effectiveness as when the device produces a clinically significant result, again, when the device is used according to the labeling. And I highlight that aspect of labeling because that becomes a very important part of both how you look at this device today as well as how the device is marketed if it is approved.

So just real briefly, I'd like to go over the agenda for today. We begin with the open public hearing. The sponsor then will make a presentation of the PMA. We at FDA will present our review findings after looking at this PMA, and the panel deliberations would then begin. And there will be an opportunity at the Chairperson's discretion for sponsor and audience comment to the panel discussion.

And, finally, we will present discussion questions that FDA staff have prepared to help facilitate the panel deliberations, and the panel will finally make a recommendation on the PMA.

Thank you. Are there any questions?

[No response.]

DR. E. HARVEY: Thank you, Colin.

Before we go on, I'd like to introduce the newest member of our panel. His name is Dr. Donald Chatman. Dr. Chatman is from Chicago, Northwestern Memorial Hospital, and I'm sure he's going to be a valuable addition to our panel.

Dr. Chatman, we've just gone through some introductory comments from Colin Pollard, who's the branch chief for the Obstetrics and Gynecology Devices Branch.

The next step is for our open public hearing. At this time we have testimony from the National Women's Health Network. The testimony will be read by our consumer representative, Diony Young.

Diony, why don't you go to the podium? Thank you.

MS. YOUNG: This statement is from the National Women's Health Network:

On behalf of the 13,000 individual and 300 organizational members of the National Women's Health Network, thank you for the opportunity to share our thoughts

about the ThermaChoice uterine balloon therapy for treatment of menorrhagia. The Network accepts financial support from neither drug nor device companies.

The Network has had the opportunity to meet with Gynecare, the device's sponsor, and to review the results from the manufacturer's clinical studies. During the FDA's 1995 meeting to develop guidelines for testing devices to perform endometrial ablation, we recommended that studies of endometrial ablation devices must be well controlled, randomized, and enroll a substantial number of women.

Based on our review of the trial data, we believe that the ThermaChoice device is safe and effective in the treatment of menorrhagia, or excessive menstrual bleeding, and we urge the panel to recommend its approval. The uterine balloon therapy reduced the number of women who experienced excessive bleeding and reduced the number of women who experienced anemia.

Further, women who received the balloon therapy were highly satisfied with its results and reported that after the procedure, menstruation had little or no effect on their daily lives. As importantly, the uterine balloon therapy had few or no known adverse effects when compared to the surgical ablation procedure.

The Network would like to see information on five

patients who were anesthetized and available for safety analysis, but who appear not to have received the balloon therapy. We're sure that the Committee has taken note of this as well, and we welcome any data the company can provide which will give us more information about these patients. Overall, we commend the sponsor for conducting a well-designed, well-controlled, multi-center trial.

The ThermaChoice uterine balloon therapy appears to be a safe and effective, viable option for the treatment of excessive menstrual bleeding. The Network urges the panel to recommend that it be approved for use in treating menorrhagia. Thank you for the opportunity to share our perspective with you.

CHAIRMAN EGLINTON: Thank you.

Is there any other commentary from the public? This was all we had on the agenda.

If not, we can move directly to the PMA by the sponsor.

MS. ALOYAN: Good morning. I'm Susan Aloyan, the Director of Regulatory Affairs at Gynecare, which is a medical device company in Menlo Park, California. The focus of our company is on the treatment of uterine disorders. Today we'll be discussing our main product, ThermaChoice Uterine Balloon Therapy System. The device is currently

marketed in over 30 countries worldwide.

I would like to take a few minutes and introduce the people we have with us today. We have four of our clinical study investigators with us: Dr. David Grainger, associate professor, Department of OB-GYN, University of Kansas; Dr. Franklin Loffer, associate professor, Department of OB-GYN, University of Arizona; Dr. Tanya Spirtos, clinical instructor, Department of OB-GYN, Stanford University School of Medicine; Dr. John Steege, professor, Department of OB-GYN, chief, Division of GYN, University of North Carolina School of Medicine.

Also from Gynecare we have today with us Dr. Milton McColl, vice president and medical director; myself, Susan Aloyan; and Laura Pendley, manager of clinical affairs.

Following my introduction, we will have a short video of Gynecare's ThermaChoice uterine balloon therapy device. After the video, Dr. McColl will continue with a description of the device and the safety features of the device. Then Dr. Franklin Loffer will be speaking about the IDE efficacy results. We will conclude our discussion with a brief summary by Dr. McColl.

Once again, the product we'll be discussing today is Gynecare's ThermaChoice uterine balloon therapy, which is

a treatment for excessive menstrual bleeding due to benign causes in women for whom childbearing is complete.

Thank you.

[Videotape shown.]

DR. McCOLL: Good morning. My name is Milt McColl, and I'm the medical director for Gynecare, and I've had the good fortune of being involved with this device essentially since its concept with Gynecare itself over the last four or so years and have been involved with the PMA process from the very beginning when we did the original protocols working with the FDA.

As Dr. Loffer has just described in the video, currently there are four treatment options available to women with menorrhagia in the United States today. Medical therapy is typically the first line treatment, but in many women it is not effective nor well tolerated. Even though D&C is a simple and safe procedure, it's not considered an effective long-term treatment for uterine bleeding.

In contrast, hysteroscopic endometrial ablation has been shown to be a very effective treatment, but due to the fact that it's technically difficult to perform and can create significant safety issues, it has never been adopted by the mainstream gynecologists.

Even though it has been around for almost 10

years, it's currently estimated that only about 20,000 endometrial ablations are being performed annually in the United States. Now, this compares to about 650,000 hysterectomies performed annually, of which as many as 20 or 30 percent would be good candidates for ablation. Currently, a significant gap still exists in this treatment chain.

Now, what this really means is that if you are a woman today in the United States and your gynecologist is not one of those 10 percent or so gynecologists who routinely performs endometrial ablation, then it's very likely that you will only be offered these two options: medical therapy or hysterectomy. Long term, this is not an acceptable situation, and a simple yet effective therapy is still very much in great demand.

Now, in July of 1996, the New England Journal of Medicine published an article by Adam Magos(ph) and Hugh O'Connor out of the United Kingdom on the long-term efficacy of endometrial ablation. In the same issue of the Journal, an editorial entitled "Alternatives to Hysterectomy for Menorrhagia" stated that these findings confirm that endometrial ablation is an effective treatment for menorrhagia. The editors then went on to say, and I quote, "Although the work of O'Connor and Magos supports the

substitution of endometrial ablation for hysterectomy, it's only a matter of time before ablation is superseded by less invasive procedures such as balloon heating."

Now, this is what the current uterine balloon therapy system looks like today. It consists of a steel catheter with a balloon on the distal tip. The catheter is connected to the controller which has the software and the hardware for the system. During a procedure, the catheter is inserted through the cervix into the uterus and filled with a small volume of dextrose in water, 5 percent dextrose in water. Once an adequate pressure is achieved, about 160 to 180 millimeters of mercury, the device is activated by simply pushing a button.

On the front panel of the controller, the pressure, temperature, and the therapy time are displayed. At the end of the 8-minute treatment, the device is automatically deactivated and the procedure completed. The fluid is then removed from the balloon and the catheter removed.

I'd like to take just a moment or so and give you a brief history of the development of the device. The concept of balloon endometrial ablation was originally developed by Dr. Robert Neuwirth out of Columbia University in New York. A renowned hysteroscopic surgeon, Dr. Neuwirth

was the first person to publish on the use of the resectoscope for uterine surgery. It was during that time that Dr. Neuwirth realized that the resectoscope would be a very difficult tool for most gynecologists to master and decided to work on developing a simpler, safer method to perform endometrial ablation.

Almost 10 years ago, in 1988, Dr. Neuwirth initiated the first bench and hysterectomy studies for the device. Following that, he teamed up with Professor Singer in the United Kingdom and other investigators and completed a pilot study of 18 cases. Both of these studies were eventually published in the Green Journal.

Following that, Dr. Haber and Dr. Vilos in Canada performed petri studies to evaluate the best efficacy for the device and different pressure settings. Then eventually, in 1994, a large-scale international multi-center study was designed. This included 14 clinical sites in seven countries, including Canada, Australia, United Kingdom, and other countries in Europe. In total, almost 500 cases have now been performed in clinical studies with similar clinical protocols.

Among these studies, there have been no intraoperative complications and a 3 percent post-operative minor complication rate. These rates are very similar to

the results that you'll see that Dr. Loffer will be presenting later. In addition, we have completed over 3,000 cases internationally without a significant complication.

Now, these are the device parameters that have been used for most of the studies as well as for the U.S. IDE studies that we're going to be discussing soon. Each of these study parameters have been specifically determined based on the previously discussed clinical and bench data. For instance, the pressure setting of 160 and 180 millimeters of mercury was originally determined following a review of the literature to ensure that the pressure setting was in a safe range as well as incorporating some of the work by Dr. Vilos on optimal pressure settings.

The 8-minute treatment time was determined based on Dr. Neuwirth's early hysterectomy work and was later supported by 16-minute hysterectomy data studies by Dr. Anderson in Denmark, who determined the device could be safely used for an extended treatment period.

In determining the temperature settings, Dr. Neuwirth recommended the highest temperatures attainable without the fluid vaporizing or boiling, particularly if used at high altitudes. So 87 degrees was selected.

Five percent dextrose in water was the fluid chosen, mainly because it's relatively inexpensive and it's

readily available in a sterile form in most operating rooms. And, lastly, the diameter of the catheter was determined to be 5 millimeters or less so that it would not require dilation of the cervix during insertion.

Now, as you can probably tell by now, in designing this system safety was used as the number one criterion. Extensive testing was done both on the design and on the device throughout the development period and prior to clinical testing. For safety reasons, the device cannot be activated until the catheter has been filled with fluid and a minimum threshold pressure is reached.

For example, in the unlikely event that the catheter were to perforate the uterus, the balloon would not be in a confined space, and this threshold pressure could not be reached.

In addition, the controller continuously monitors the pressure and the temperature of the device. If at any time during the procedure the pressure or the temperature are outside the normal operating range, the device will automatically terminate and the procedure--the device will deactivate and the procedure will terminate.

Fail-safe mechanisms have also been built into both the hardware and the software. For instance, instead of just one thermocouple on the heating element, there's

actually two thermocouples located inside the balloon. The algorithm of the software is such that not only is the 87-degree temperature measured, but the two temperatures of the two thermocouples are compared against each other. So if one of the thermocouples wasn't working, again, the device would immediately deactivate.

Lastly, the balloon itself was designed to minimize any chance of balloon rupture. First you must understand that the balloon inside the uterus acts very much like the tire tube inside of a tire. In other words, the pressure is not really being held by the balloon; it's being held by the surrounding uterus. In addition, in order for a balloon rupture to occur, the balloon must be under significant tension during the procedure.

As you can see here, the balloon is actually designed much larger than the uterus itself, than uterine volumes. Typical uterine volumes during our procedures were shown to be in a range of about 8 to 15 cc's. So even at the maximum balloon volumes of our recommended procedures of 30 cc's, the balloon itself is not under tension.

In this slide, we've actually taken the balloon and inflated it with more than 10 times the recommended volume, and you can it withstands the pressure very well.

Now, even if a balloon rupture did occur, an

animal study in which the balloon was intentionally ruptured with scissors indicated that the device would, first, immediately deactivate as anticipated; that the fluid would exit through the path of least resistance, which is through the cervix; and that due to the high blood flow to the area, there was no injury noted on histological examination.

Now, following completion of these early clinical studies, we approached the FDA in 1994 regarding the marketing of this device in the United States. At that time we were informed that this product would be subject to the premarket approval process. So working closely with the FDA at that time, we submitted an IDE feasibility study protocol, which was eventually approved in early 1995. That study was then completed in October of 1995.

The investigators involved with that study were Dr. David Grainger and Dr. John Steege, who are both here with us this morning. The objectives were: number one, to identify the distribution of thermal effects on the uterus, and in particular, to see if there were any thermal changes on the serosal surface that might affect surrounding viscera. In addition, we quantified the depths of endometrial destruction and identified any complications that might occur.

So essentially what we did during this feasibility

study was during a laparotomy for a hysterectomy, abdominal hysterectomy, thermocouples were placed at different places on the uterus, including five around the serosal area and into the myometrium into the endometrium. The balloon catheter was then inserted and inflated with fluid and the device activated.

Now, for this feasibility study, we treated eight patients, and one patient was used as a control. In that patient, the device was actually inserted but not turned on. All patients had to meet specific inclusion and exclusion criteria. Following the laparotomy for hysterectomy, 12 thermocouples were placed in strategic places throughout the uterus, the balloon catheter was placed and filled with fluids, and the 8-minute treatment cycle was completed. The catheter was then removed, the hysterectomy completed, and the specimen sent to pathology.

Now, this graph represents the average serosal temperatures during the UBT therapy system. The X axis represents the treatment time through 8 minutes; the Y axis represents the temperature in degrees Celsius.

As you can see, this blue line represents the control unit, the average temperatures, serosal temperatures in the control, that one control that we discussed earlier. As you can see, there was no rise. Those are very stable

temperatures.

In comparison, the serosal temperatures rose very modestly, only about 2 degrees Celsius, during the 8-minute cycle. Interestingly, this data corresponds very well with the data that Dr. Anderson in Denmark, as I mentioned earlier, had done with 16-minute treatments which showed that this plateaued out at about 4 minutes and stayed consistent throughout the 16-minute treatment time. The device certainly was not creating too much heat on the serosal surface which might injure surrounding viscera.

Now, this is a typical hysteroscopic view of what the uterus looks like prior to endometrial balloon ablation. As you can see, it's a normal looking uterine cavity, and the endometrium is very viable and pink.

This is a typical post-treatment procedure using the balloon therapy system. You can see the endometrium is well coagulated and blanched.

Now, following the hysterectomy, as I mentioned, the uterus specimens were taken to pathology and gross histological exam was looked at. First of all, you can see on this gross look that the endometrium is uniformly coagulated throughout, where the cervical area is spared. In addition, histologic examinations occurred. We took slices of these tissues and looked under histological

examination and noted that the injury was uniform through the endometrium, through the basal layer, and into the myometrium.

So, in conclusion from the safety study, we concluded that the balloon system was simple to perform, as we expected. There was a minimal rise in serosal temperatures. There was uniform destruction of the endometrium through the basal layer and into the myometrium. Most importantly, there were no complications from it, and it allowed us to feel comfortable working forward with the FDA to develop an IDE efficacy trial.

At this time I'm going to have Dr. Loffer present the results from our efficacy study. I would like to make one comment about the data that we are presenting today. At the time that we put together the information that we've included in the package for you, we had about 85 percent of our one-year data complete. We had completed all follow-up on--six-month follow-up on all patients, and 85 percent of the patients had completed their one-year follow-up. As of today, we have completed all the one-year data on these patients.

Now, the data we will present with Dr. Loffer today will be just the 85 percent data that we submitted to you about six weeks ago. In addition, there is one

correction. In talking with the FDA over the last couple of days, they have asked us to make one adjustment to the success rates. Two patients--one patient in the balloon group and one in the rollerball group--had had hysterectomies for menorrhagia, and both of those patients have now been added back to your data for success rates, as well noted in the slides here, and those patients are now considered failures in that group.

So at this time, I'd like to invite Dr. Loffer up to speak on the efficacy data.

DR. LOFFER: Thank you, Dr. McColl.

Members of the panel, ladies and gentlemen, I'm Franklin Loffer. My travel and expenses to attend this meeting were paid for by Gynecare. I'm one of their investigators, and I'm a member of their Medical Advisory Committee.

The objectives of this study were to identify any complications or adverse events that might result from the use of the UBT system. It was also to evaluate the safety and effectiveness of UBT and to compare it against the rollerball endometrial ablation method. Our primary endpoints were diary scores, both pre- and post-treatment. Our secondary endpoint was a quality-of-life measurement.

Two hundred and seventy-five patients were

randomized at 14 clinical sites--two in Canada and 12 in the United States. At each site, patients were stratified by age, either over or under 40, and then randomized to either the UBT or the rollerball. Diary scores were obtained at baseline, 3, 6, and 12 months, and quality-of-life's were obtained at baselines, 6 months, 12 months, and will be followed for 2 and to 3 years.

Our study sites were geographically distributed over this country and Canada. They were composed of individuals in university settings and in private practice settings. All of the hysteroscopists in this group were experienced in the rollerball technique.

Our inclusion criteria were patients who were at least 30 years of age and were pre-menopausal. They had to have had a documented 3-month history of menorrhagia. They had to have had a documented failure of medical therapy. Their childbearing had to have been completed. A biopsy of the lining of the uterus and a Pap smear were negative. Uterine sizes that were included were 4 to 10 centimeters, and patients were required to have a diary score of at least 150. In the scoring system that we used, 100 was equal to menorrhagia or roughly a blood loss of 80 milliliters per cycle.

The scoring system that we used was Higham's,

published in the British Journal of Obstetrics and Gynecology in August of 1990. It was a visual scoring system that was validated. We required specific pads to be used to do away with the variable of absorption.

Exclusion criteria were septate or bicornuate uteruses. The heating element of the catheter, if it fell on one side or the other, would not allow treatment of the opposite side, although fibroids, small fibroids and those that are primarily intramural most likely could be treated. For the sake of clarity, some uterus fibroids were excluded. Patients could not have a genital or urinary tract infection, nor any pre- or malignancy, sensitivity to latex, or previous endometrial ablation.

There was no timing of the cycle. They could be done at any time during the menstrual cycle. There was no hormonal pre-treatment used to thin the endometrial surface. There was a 3-minute pre-procedural suction curettage designed--or built into the study to make endometrial ablation by the rollerball simpler. The anesthesia was determined solely by the investigator after discussion with the patient. Balloon ablation was done for 8 minutes, and the techniques for rollerball were done using standard equipment and standard techniques.

Looking at the demographics, there was no

statistical difference between groups. Ages, mean basal diary score, which I would point out were really quite high at 500--and if you recall, our inclusionary criteria was 150, menorrhagia with this system demonstrated at 100. Some of these patients actually were in the several thousand in their scoring.

The obesity was similar between groups. The years of menorrhagia were similar. These patients all had long-standing menorrhagia, 9.9 to 10.1 years. The hemoglobin levels were similar. Uterine cavity length was the same, similar, and the days of bleeding.

Further, race, the position of the uterus in the pelvis, the presence or absence of premenstrual symptoms, the degree of dysmenorrhea, and the inability to work outside of the home because of heavy bleeding were statistically the same in all groups.

The intent-to-treat group, there were 275 patients that were randomized. Safety evaluable group dropped to 260 who were actually anesthetized. By and large, the 15 patients who dropped out did not want to participate in the study. There were five patients that were anesthetized but not treated. One of those was in the rollerball group. She was not treated because of a perforation that occurred. There were two patients, one in each group, who were

identified to have a submucous fibroid which was exclusionary criteria. There were two patients who were not treated in the uterine balloon therapy group. The reasons that they weren't treated was that 30 cc's of D5W was placed in the catheter, and the pressures required to activate the systems could not be achieved, and, therefore, the procedure was not carried out.

Of the 255 patients that were treated, our 6-month efficacy number is 245, and as Dr. McColl told you, today we will be discussing the one-year efficacy evaluable group, 207 patients, which is 85 percent of our total patients that we can evaluate.

Looking at the device-related adverse events, they were primarily in the rollerball group. There were no intraoperative adverse events in the UBT group. In the rollerball group, there was one uterine perforation, two fluid overloads, and one cervical laceration.

Post-operative adverse events in the UBT group, there were three endometritises, one urinary tract infection. There was one patient who had post-coital bleeding. In her workup, she had a cervical polyp and was identified to have chronic endometritis. It's questionable whether this was related to the UBT therapy, but it was included as an adverse event.

In the rollerball, there was an endometritis, hematometria, and a post-ablation tubal sterilization syndrome.

Looking at the types of anesthesia, these were determined by the investigator in conjunction with the patient. There would appear to be a predisposition to use general anesthesia for the rollerball and less anesthesia for the balloon patients. Eighty-four percent of the rollerball patients had general anesthesia. Only 53 percent of the UBT patients had a general anesthesia. IV sedation, paracervical block, regional, and others all showed a trend toward less anesthesia with the balloon system.

Looking at the issue of post-operative pelvic cramping, this was within 48 hours. There was more cramping in the balloon system. This is statistically different from what the rollerball group showed, but I would emphasize it's not a clinical difference. All of these patients were discharged home on the same day. None were kept overnight.

This is not an easy slide to evaluate for several reasons. One, there was no consistency of anesthesia between these groups. Secondly, there was not a standard protocol for managing pain in the post-operative period. And, thirdly, the figures that are shown here were derived from the adverse event sheets that the study monitors, study

coordinators kept track of. These were not patient ratings. These were done by an observer. So there is statistically significant difference, but there certainly is not a clinical difference.

Looking at procedure times, there is a statistically significant difference between the balloon and the roller technique. I frankly would have expected this to have been larger. However, looking at the fact that all of the investigators in the rollerball had been doing this for a long period of time, were experienced, their operating room staffs were experienced, probably accounts for--even though statistically different, maybe not a greater group. We all had a learning curve when we were doing the balloon therapy.

This slide is the primary endpoint of this study, probably the most important slide I'm going to be showing you. A couple of things I'd want you to understand: Recall that this is 85 percent of our one-year efficacy evaluation. At six months, these are the same patients. This is the same 85 percent that we're going to compare at one year. So they are the same patients being compared against themselves.

There is virtually no change, diminishing of effect of the efficacy of this procedure from six months to

12 months: 78.9, 81.6, 85.7 in the roller, to 85.7. It's important to realize that, in looking at the very same patients, there doesn't seem to be any trailing off. We have the same consistency. Therefore, the one-year success rate percentage difference of negative 4.1 percent, a 95 confidence interval, the range is negative--ranges from negative 14.1 to 5.9. This was well within the study criteria as established for this study.

The other point that I would remind you of, menorrhagia by the scoring system used was 100. To make it more difficult to achieve success, we defined success as 75 or less.

The FDA asked us to look at success rates related to the patient's age. I assume this was because it's the general clinical impression of gynecologists that older patients are more easily treated and achieve better results than younger patients. The aggregate mean, the bar graphs that I showed you in the preceding slide, shows 85.7 percent in the rollerball and 81.6 percent. There is a considerable consistency in the balloon group: 81.6 up to in the greater than 40 and down to in the less than 40.

The real variability in this slide is in the rollerball group. The aggregate mean for all ages, 85.7, dropping down to 80.8 in greater than 40 and going up to

91.3 in the less than 40.

I think there is--I have a suspicion if you looked at other age groups, you would not have seen this variability. I as a practicing gynecologist doing a lot of rollerballs don't see in my own hands--and I don't really believe that my patients at the age of 40 do poorer than do those patients that are younger than 40, and that's what this graph suggests. But bear in mind you're looking just at an arbitrary figure of 40 years of age.

I think further to emphasize that that's probably a statistical aberration is when you look at the mean percentage decrease in diary scores--this is the aggregate mean at one year--you see very little change in either group. So the mean percentage decrease in diary scores changes very little looking at age greater than 40 or less than 40.

Looking at quality-of-life issues, our secondary endpoint, satisfaction rating was great: 86.9 and 87.4 percent. Patients were very satisfied with the results they've obtained. I think it's interesting, if you look at our failure rates, as defined by the very strict criteria that were set up, you see approximately a 14 percent, quote, failure rate in the rollerball and about 18 percent in the thermal balloon system. And even though there was 14

percent in each group that technically failed, at least by the criteria that we used, only 4.7 and 0 percent were dissatisfied with the procedure. You could have had a 90 percent reduction in menstrual flow and still have failed.

Looking at dysmenorrhea, the vast majority of patients had a decrease in dysmenorrhea. There were some, roughly a quarter, that had no change. Very few patients in either group showed an increase.

With regard to the inability to work outside of the home due to heavy menstrual flow, over a third in each group were unable to leave the house. This dropped down to a very small number in each group.

It would appear that this is a valid study. Both techniques achieved significant reduction in menstrual bleeding and a significant improvement in quality of life. And the most important thing is the results appear to be stable and consistent over time.

Thank you very much.

DR. McCOLL: Thank you, Dr. Loffer.

Well, just to briefly summarize our presentation, looking back at the treatment options available for menorrhagia, clearly hysteroscopic endometrial ablation is actually an excellent procedure, particularly if done in the hands of an experienced hysteroscopic surgeon. But,

unfortunately, in the United States today, most women really do not have access to that technology, at least not a majority of them. So there still is a significant need for a simple, effective treatment, safe and effective treatment.

Going back to the history of Dr. Neuwirth in 1988 and all the work that we've done since that time, there is now a very long history with many, many studies that have been conducted on this device as well as large volumes of data. I think the PMA itself was 10,000 pages that we put together for this particular device.

In addition, there have been no significant complications with the device. It's now been used in over 3,000 patients worldwide. And, lastly, as Dr. Loffer just showed, multiple studies, including the IDE study, show that the device is very consistent over time, some of the international studies now going out two and three years showing the same consistency of results.

So today we believe that the uterine balloon therapy is a safe procedure. We believe it's an effective procedure and that it's a viable alternative to rollerball and hysterectomy in properly selected patients.

Now, I would like to just emphasize the part on properly selected patients. We're very sensitive to the FDA's concerns about making sure the right patients are

treated, so we have put together a training program for our physicians to use when this device is hopefully approved eventually someday. I didn't mean to say it that way.

[Laughter.]

DR. McCOLL: Anyway, as far as our indications for use as listed here, the ThermaChoice balloon system is a treatment for excessive menstrual bleeding due to benign causes in women for whom childbearing is complete. The key contraindications are a patient who is pregnant or wants to become pregnant; a patient who has a history of latex allergy; a patient with a known or suspected diagnosis of cancer, particularly of the reproductive tract; any anatomical or pathologic condition in which a severe thinning or weakness of the myometrium could exist; lastly, an active genital infection.

So that concludes the presentation from the company side. We thank you for your time this morning.

CHAIRMAN EGLINTON: We're thankfully running ahead. We're scheduled at this point to have a break. Is there anyone on the panel who demands a break? Can we press forward?

Okay. We'll go on with the FDA summary. Yung Pak?

MR. PAK: Good morning. My name is Yung Pak, a

mechanical engineer and lead reviewer for the PMA before you today.

Next slide, please.

I'm going to introduce FDA staff who helped reviewing this PMA. Steve Retta and myself reviewed the engineering portion of the PMA, including mechanical failure and thermal analysis. Kathy Daws-Kopp reviewed the electrical safety and electromagnetic compatibility of the device. John Murray reviewed the software documentation. Dr. Brian Harvey reviewed the clinical study, and Richard Kotz reviewed the study design and statistical analysis of the clinical study.

Next slide.

And the following people are the other FDA staff who helped reviewing this PMA. As you can see, we utilized all the necessary people to assess the safety and effectiveness of the device.

Next slide.

This summarizes an overall view of the FDA presentation. I'm going to spend about 15 minutes discussing the preclinical study, including toxicology, sterilization, and engineering analysis. Next, John Murray is going to spend 10 minutes discussing the software because it plays a very important role for the device's function.

Then Dr. Brian Harvey will spend 10 minutes discussing clinical review findings. Finally, Richard Kotz will spend 10 minutes discussing the statistical analysis.

Next slide.

Since the sponsor went over the device description and operating principle, I will go over safety features of the device because they play an important role in preventing some of the potential hazards. The device can be only activated when the balloon pressure is 150 mm of mercury. It is recommended that the pressure be stabilized for at least 30 seconds and the recommended operating pressure is between 160 to 180 mm of mercury.

The software monitors the temperature and pressure and directs the heater to shut off in case the operating parameters are outside the boundary. As you can see, if the high temperature is higher than 95 or lower than 75 Centigrade, it shuts off the heater. If the pressure is higher than 210 or lower than 45, the heater shuts off. There are warning alarms at different temperature and pressure settings to alert the users.

Next slide.

There is an electrical heater circuitry that cuts off the heater independent of the software. The heater circuitry has voltage sense, current sense, and heater on

time sense circuits. The microprocessor normally generates electronic signals to the heater circuit to control the temperature, and if there are no signals from the microprocessor, the circuit will turn off the heater in seconds.

Next slide.

This summarizes the overall engineering strategy we took to review the PMA. We analyzed each device component for any potential failures. We also looked at the whole system for its potential failures. We then identified potential hazards that may occur with component failures. We reviewed all the bench testing the sponsor provided to see whether the tests are done properly and adequately. We also studied what will happen when the software fails and see whether there are any hardware backups. Finally, we looked at human factors to see if the device is user friendly.

We focused on failure analysis for the following: the balloon, thermocouple, heating element, pressure sensor, reliability of the hardware, software control, electrical safety, electromagnetic compatibility, and material safety.

Next slide.

This drawing shows the distal end of the catheter where the balloon is located. As you can see, Item 1 is a

balloon. Within the balloon is number two, which is the heating element, and it's surrounded by two thermocouples in Item No. 3, top and bottom.

The balloon is located at the distal end of the catheter and attached to the catheter tube with suture winding and glued with a sleeve. We evaluated the following bench testing for the balloon strength and design validation. The leakage test is being done by the sponsor on each manufacturing lot for quality assurance purpose.

Next slide.

For thermocouple analysis, we reviewed the thermocouple specs for its accuracy and response time. We reviewed the bench testing, confirming the accuracy of the thermocouple, and comparing temperature accuracy to other types of thermocouples. There is a backup thermocouple in case of primary thermocouple failure, and the software monitors the temperature and shuts the system down if the temperature is outside the boundary.

Next slide.

We looked at the design of the heating element which is a resistance wire wrapped around the ceramic core. The software monitors the temperature of the heater to see if there are temperature changes and shuts off the heater if the temperature is outside the boundary. In case of

software failure, the electrically driven hardware automatically shuts off the heater in seconds. Also, we evaluated the bench testing which confirmed the temperature reading, pressure reading, and balloon condition right after when the hardware backup shuts off the heater.

Next slide.

We looked at the pressure sense spec for its accuracy and response time. Please note that there is no safety mechanism to release the pressure in case of high pressure build-up in the balloon. But we believe that there will be no significant pressure build-up when using the device. We know that significant pressure can build up only when the water inside the balloon boils, but this is very unlikely event since there are both software and hardware backups that will prevent this mishap.

Next slide.

The software is designed with watchdog that checks the software control in case of software errors. This is critical part of the device control, and John Murray will provide more software details immediately following my presentation. Besides software control, there is an automatic hardware backup system that will cut off the heater in case of software malfunction as I described earlier.

Next slide.

Electrical safety and electromagnetic testing met industry-recognized standard such as IEC--which stands for International Electrotechnical Commission--601 and 801.

Next slide.

Biocompatibility and microbiological testing are done satisfactorily to ensure the material safety. Accelerated shelf life is completed for the catheter and balloon, and real-time shelf life is going on now. The proposed shelf life is 13 months, and currently we are working with the sponsor to establish a baseline for real-time shelf life.

Next slide.

Finally, we looked at the human factors to see if the device is user friendly. We evaluated if the display and markings are large and clear enough to see. We evaluated if the directions for use are easy to follow and if components are easy to connect when setting up the device for use.

Next slide.

In conclusion, we believe that the sponsor adequately tested the component for its failure modes and design validation, and we believe that the device is user friendly. We are currently working with the sponsor to

resolve some of the minor technical issues.

Thank you. This concludes my presentation of the Gynecare ThermaChoice PMA. I would like to ask panel members to wait for any engineering questions until John Murray finishes his presentation about the software.

MR. MURRAY: That was a pretty quick 15 minutes.

Good morning, everybody. My name is John Murray. I'm a software engineer, and I work in the Office of Science and Technology here in the center. Currently I'm the team leader for software and intelligent medical devices, and I did conduct a review of the software component of this device. The first item I have here on the first page is I want to remind everyone--and this is my opinion--that software plays a critical role in the operation of this device. So the first thing I think is important is to tell you what I found out from reviewing the device as far as normal operation, and you can compare that to what you think it's going to do from a clinical perspective.

This software controls the sequence of operations using operator prompts and threshold set point. It will not allow the heater to turn on until the pressure is greater than 150 mm of mercury. And there are established high pressure, low pressure, low temperature, and high temperature set points which are controlled by the software.

During the entire operation of the device, the software will measure and display the current temperature in the balloon. It will also measure and display the current pressure in the balloon. The software automatically controls the preheat and the therapy temperature for the entire operation. The software automatically calculates and displays the preheat times and the treatment times. That would be the 8-minute treatment time and the up to 4-minute preheat time. In addition, it automatically calculates the therapy time and will shut down the heater when therapy time reaches 8 minutes.

I guess one point that I noted was that software has no control at all over the balloon pressure. That's completely controlled by the operator.

In addition to normal operation, this device also provides alert and hazard conditions that are controlled by the software. In the event of an alert or hazard condition, which would be high temperature or high pressure, low pressure, low temperature, the machine will actually provide operator instructions that will allow the operator to place the device in a safe condition and to place the patient in a safe condition. For example, it might tell you to remove the catheter.

In addition, to get the operator's attention in

the event that they are not watching the panel, the software automatically provides audible alerts that will get the operator's attention.

As I said before, all these alarms and all these hazard conditions are based on various pressure and temperature value set points. I guess the most important feature here is that in the event of one of these hazard conditions, the software will actually shut down the catheter heater and, therefore, there will be no more heat added to the balloon.

Two things that I noted while doing this review was that in the event of a hazard condition, the operator will be required to completely power off this device in order to resume therapy. There's no way--there's no feature in this device that allows them to resume therapy after a hazard condition. In addition, I noted that if you for some reason lose power with this device, the device will not return to the point of therapy that it departed. In other words, there's basically no fail-safe condition here that's going to take you back to where you left off. You're going to have to start right over. Hopefully this is covered by the operator label and training.

I think, like Milt said, they've worked on this project for a long time, and there are many, many details

involved with the software. And it's just not physically possible to review everything that they've done, so we put together a plan about how are we going to go about getting a level of assurance and a level of confidence that the company itself has the capability to actually design and build and test software. So the primary components of this review included the software requirement specification and the software validation, verification, and test.

The concept here was to address two primary questions. The first question is: Is this software the right software for this clinical application? In other words, do the software requirements correctly identify the software functions that are required by the clinical use of this device? That's the clinical side of the issue.

On the engineering side, we take a look at, well, now that we've defined the software we need, did we, in fact, build the software correctly? Did we properly use our quality control system, our design control system, and our GMP system to build safe and effective software?

I think this issue at the top of this page is kind of out of order because I wanted everybody to be reminded that this is a level of confidence review. There's no way for me to go look at every detail they have. So what I do is, going through this review I establish a confidence that

their system is appropriate for the risk associated with the software in this device. And the primary key to doing this is the software requirement spec which I have labeled as the gateway from the clinical to the engineering.

I went through the software requirements document, and I documented every place that the software was going to provide some information or some control to the clinical operator, and then I presented this information to the medical staff within CDRH, Dr. Harvey, and asked him to review this and tell me whether or not this was the appropriate indication, temperature set points, pressure set points, and automatic shutdowns that he would expect with this clinical application. And he said he believed that it did.

So I guess, in summary, what we did was we reviewed the software requirements for this device from the clinical side. We also reviewed the software requirements from the engineering side to make sure engineering details were implemented properly, and based on the requirements actually went through and reviewed the validation test procedures that Gynecare provided to us.

As a result of this review, some deficiencies were identified in the process. Gynecare was notified, and all these deficiencies have been corrected except for one item.

And we talked to Gynecare, I think it was on Thursday, and this remaining deficiency is resolvable, and Gynecare and the FDA have agreed to work together to resolve this issue. And the item is really related to the software product baseline; in other words, there are some small deficiencies in the actual paperwork that described the software design as it currently exists. We would like to have that baseline established so it's absolutely perfect before this product goes to market in the U.S.

One thing I noted in my review which didn't make sense to me--but I'm an engineer, so this might not have a problem for you--when this machine displays the time that's elapsed since the start of the procedure, the actual therapy time is not displayed. What is displayed on the device is the total amount of time from the preheat time and the therapy time. So if it takes the device 3 minutes to heat up, when you get to end of therapy you're going to have 11 minutes displayed. So the operator is not really going to have an indication of the actual therapy time that's elapsed.

I don't know if this is a problem, but I'm thinking of--I always think of worst-case conditions. That's the way I think. If you lose power or something happens to the device in the middle of therapy and you don't

know exactly how long the device has been running, you will not know how much therapy has been applied. So when you go back to redo the therapy, you won't have any idea what that was. That's just an engineering observation of a clinical thing which I claim no knowledge of.

The conclusion is the documentation provided by Gynecare indicates that the software component of this device is appropriate for its intended use, and based on software considerations, I recommend conditional approval of this PMA until the software product baseline deficiency is corrected.

Thank you.

MR. PAK: I'd like to ask panel members if there are any technical questions related to engineering and software.

DR. SHIRK: Yung, I've got one question, and Mr. Murray alluded to it. There's no way to keep the clinician from adding water or fluid to the system that I can see during the procedure. The device obviously is set at a certain pressure, and that's determined initially by the clinician as he fills the balloon. Because of the heating of myometrium, the myometrium relaxes, and then there's a significant drop in the uterine pressure during the procedure. And at this point, I'm not sure whether that

would be harmful or not, but--or if you had a partial perforation, if the clinician added fluid slowly to the system to keep the temperature from kicking off, whether there could be a clinical problem with this.

MR. PAK: What I know is there has been a European study that during the therapy fluid has been added, and it has been shown that there is no problem, you know, keeping the temperature and pressure. I don't know if I can ask Dr. Harvey to comment on that, maybe, the European study that has been demonstrated. Do you know anything about that, Dr. Harvey, or--Dr. McColl?

DR. McCOLL: Dr. Shirk, I think if I understand your question correctly, you're asking: Is it possible to actually add fluid during the procedure while the procedure is undergoing? I guess the answer is yes, it is actually possible, just like it's possible to treat a patient twice if you wanted. Clearly, the device labeling, it's very well delineated that you should never add fluid during the procedure. That's first of all. We think that's a very important factor here.

Number two is actually the way the software is written it's such that even very slight fluctuations in temperature would actually shut the procedure down immediately. So by adding even small amounts of fluid,

we've found that you actually would shut--typically shut the device off because of the slight fluctuation in the temperature, as well as pressure. So if you affect the pressure or you affect the temperature of the fluid, the device would shut down immediately.

But you are correct that there are ways, if you wanted to, you could potentially, if you intentionally wanted to override the system.

DR. BLANCO: Before you go away, following up on that, is there a recommended maximum amount of fluid that you're going to put in your labeling? And what is that that gets put in to achieve your pressure after which you should not--you know, you recommend that you not continue with the procedure?

DR. McCOLL: Right. The studies that we did, as Dr. Loffer mentioned for the U.S. study, included criterion such that not greater than 30 cc's could be used in volume of uteruses, and that's what--the current proposed labeling that we submitted to FDA is around the same parameters that we ran both our international studies, which were on that same category, as well as our U.S. studies.

I would like to make a comment that some of our international investigators have investigated looking at using the device in larger volumes, and they have shown

actually very good clinical results.

Unlike hysteroscopic ablation where you increase the size of the uterus and the surface area increases inside the uterus, with this device it's really not as relevant because all you're doing is creating a larger volume of--or heat sink of fluid which can typically treat larger fluids--or larger surface areas. So we have labeled the device specifically from the use, the same that we had from the IDE efficacy study.

MR. MURRAY: My name is John Murray. Milt used the words "slight changes in pressure." And to start this procedure, it requires 150 mm of mercury, but to shut it down it's 45. The word "slight" I don't think is the right word here, but I just wanted you to know what that number was for your use.

Thank you.

DR. NEUMANN: Let me ask some of these. If they're inappropriate, please let me know.

One question that came to mind is that it is possible to introduce some air into the system, perhaps some air in the syringe, or the coupling between the syringe and the probe is not adequate. What happens when there's a little air in the balloon?

MR. PAK: Okay. First of all, before you use the

device, you have to get what's called the--you have to use a syringe. You have to inject the fluid inside the balloon, and you have to take the fluid out to remove any kind of bubbles that may be in the balloon. So that is sort of a preventive procedure that you have to do, and so we figure that there shouldn't be any bubbles inside the balloon. In case there is a bubble, we think that it may give you a false reading on the pressure, so the system may shut off.

DR. NEUMANN: I don't think that would happen. I think it's more a case of heat conduction. Pascal's law will say the pressure is the same in the fluid as in the air. But what about the thermal properties? What if the heater, for example, really worst-case, the heater is in a pocket of air?

MR. PAK: So you're worried about if the temperature is going to overshoot, basically, because--

DR. NEUMANN: I don't know what will happen. I'm just asking you if you've investigated that.

CHAIRMAN EGLINTON: Dr. McColl?

DR. McCOLL: Just a couple comments to go back on Mr. Pak's comment about the priming of the device, I think what he was talking about. The labeling for the device is such that it's recommended to prime the device--in fact, required to prime the device before you actually insert it.

What that essentially does is purge the system of air bubbles much like you do with a syringe prior to injecting into a patient into the venous system. So that's the first thing. So typically, even if you did--even if you didn't probably follow that correctly, it would be very small volumes of air that you might inject into the balloon. That's the first thing.

The second thing, I think the only effect possibly would be--because we've actually seen this in demonstrations where we don't prime the balloons as quickly or as well as we'd like to--small amounts of air can actually be in the top of the balloon. But typically in this procedure, because you have such a large surface area that's occurring there, number one, it wouldn't be a safety issue, I don't think. Our experience has been if you actually did have it here in an air system, the device is a very, very small, delicate wire, and the wire itself, as I'm told by engineers, would burn out much like a short in a circuit breaker you'd have, where if there's too much current through there without a fluid in there to cool it, it would immediately short itself out and the device would shut down. It's almost a built-in safety circuit breaker.

So, first of all, that's probably what would happen if there was an air pocket. The second thing is that

as far as efficacy, the only thing I can see different is a very small balloon, was that you might have a little bit of area of possibly slightly undertreated area as compared to the large volume of the uterus, and efficacy-wise I don't think it would have a long-term effect on the treatment.

DR. BLANCO: The clinical investigators that have used the device, have you all noticed if there has been air after it in any of the procedures you've done, if there's been some bubbles of air when you pull it out?

DR. E. HARVEY: Excuse me. I'm sorry to interrupt. We probably should continue with the remainder of FDA's presentation. We can address some of these questions later on in the panel deliberations. Thanks.

I believe Dr. Brian Harvey is next.

DR. B. HARVEY: My name is Brian Harvey, and I am a medical officer with the FDA's Office of Device Evaluation, and I'm the primary clinical reviewer on this premarket application. Earlier you heard from the sponsor that has provided an overview of both the world clinical experience for the Gynecare ThermaChoice Uterine Balloon Therapy System, as well as the clinical data obtained under the IDE. At this point, I would like to highlight the important aspects of this UBT clinical data from the FDA perspective.

Next slide.

As we had heard earlier, there have been over 541 cases completed internationally, with no intra-operative or major post-operative complications. Of these 541 cases that were presented in the original PMA application, there were 18 minor post-operative complications, or about 3.3 percent.

Of note, of these 5 percent of patients--in that international experience, there have been 5 percent of the patients who have had repeat endometrial ablation procedures and 6 percent of patients who have gone on to have hysterectomies.

In the U.S. feasibility study, conducted under an IDE, the Gynecare ThermaChoice UBT was performed on eight women who had previously decided to undergo hysterectomy. As we have heard previously, the UBT was performed just prior to uterus removal. A total of 12 thermocouples were placed on the external and internal surfaces of the uterus in order to measure the serosal, myometrial, and endometrial temperatures during the UBT ablation procedure. After hysterectomy, histology was performed on the uterine tissue and correlated with macroscopic observations.

Histology revealed average necrosis of 0.8-4.4 mm in depth. The sponsor has presented the data supporting the conclusions that the UBT produced a minimal rise in serosal

temperatures and uniform destruction of the endometrial tissue.

In the U.S. pivotal study, conducted under an IDE, as you've heard from the sponsor, they provided the details of how this--the design of this clinical trial, comparing the ThermaChoice UBT therapy to the rollerball endometrial ablation for treating women with menorrhagia. And as they had described, when this PMA was submitted, there was 100 percent of the 6-month follow-up data and 85 percent of the 12-month follow-up data. This correlates to 109 patients who had undergone the UBT therapy. And of note, just to highlight what's going to be coming up in the statistical presentation, in the original statistical analysis in the IDE it was determined that you needed 108 patients with UBT therapy in order to have adequate statistical power in order to demonstrate the difference and prove the null hypothesis; therefore, even with only 85 percent of the patients having had 12-month follow-up, there's still adequate power to make that determination. And now, as we've heard from the sponsor, there is 100 percent follow-up at 12 months.

Also of note, the study design, it was not designed to have adequate power to actually stratify patients by age, so that will be coming up later on in one of the discussion questions.

In this IDE study, the sponsor had proposed the following list of potential adverse events that could be associated with the UBT endometrial ablation, and those potential adverse events were: perforation or rupture of the uterus, full thickness burns of the uterine wall or burns of the adjacent tissue, heated liquid escaping into the anatomical structures adjacent to the uterus, electrical burns, allergic reactions to latex, blood loss, infection, hematometra, pregnancy, masking of subsequent cancer, and post-ablation tubal sterilization syndrome. However, in this IDE pivotal trial, there were no intra-operative complications, and there were no major post-operative complications.

As we had heard earlier, there were five minor post-operative complications which represent 3.7 percent of the UBT patients, and these were three cases of endometritis, one urinary tract infection, and one case, which may not be device-related, of an endometrial polypoid inflammation with post-coital bleeding.

Next slide.

In the pivotal trial, the primary endpoint was based upon a diary score proposed by Higham and associates at the Royal Free Hospital in London and published in the British Journal of Obstetrics and Gynecology in 1990.

Next slide.

In their study, women were provided with Tampax or Kotex Fems super-plus tampons and Kotex Simplicity size 2 towels, which they used and collected in plastic bags during their menses. The amount of menstrual blood loss was determined from these tampons or towels by the method of alkaline haematin determination, and a pictorial blood loss assessment chart score was recorded both by the patient and their gynecologist. This slide is the pictorial blood loss assessment chart from their original journal article.

Next slide.

The menstrual blood loss, abbreviated MBL, was then correlated with the pictorial blood loss assessment chart, abbreviated PBAC, as shown in this graph from the 1990 publication. We can see menstrual blood loss on the Y axis versus the pictorial blood loss assessment chart on the X axis. And with n equal to 122 monitored cycles, the r value for this correlation is approximately 0.9 percent.

At the end of this article, the authors concluded there was a good relationship between the menstrual blood loss experienced by women during menses and the pictorial blood loss assessment chart score. By taking a score of greater than or equal to 100 as diagnostic of menorrhagia--and this corresponds to a blood loss of approximately 80 ml

of blood per month or greater--the pictorial blood loss assessment chart method was found to have a sensitivity of 86 percent and a specificity of 89 percent using the scores recorded by women, and a sensitivity of 86 percent and a specificity of 81 percent using the scores recorded by the gynecologists.

Next slide.

Before I review the effectiveness data for the pivotal trial, I would like to highlight both the exclusion and inclusion criteria for this pivotal study since this information will have direct bearing on the medical device labeling for the Gynecare ThermaChoice UBT System. In this trial, the inclusion criteria were: a diary score of greater than or equal to 150; age greater than or equal to 30 years and premenopausal status; at least 3 months diagnosis of documented menorrhagia; documented failure of medical therapy; patients should have completed childbearing with continued contraception post procedure; negative endometrial biopsy and Pap smear prior to the procedure; and a uterine cavity equal to or greater than 4 cm in size, but not greater than 10 cm.

Next slide.

The exclusion criteria for the trial were: septate or bicornuate uterus; submucous fibroids or polyps;

genital or urinary tract infection; malignant or premalignant uterine lesions; a sensitivity to latex; or previous endometrial ablation.

Next slide.

Based upon the pictorial blood loss assessment chart score I described previously, a score of 100 or greater was diagnostic of menorrhagia, and the inclusion criteria of the study was a pre-treatment diary score of greater than 150. Therefore, a treatment success was defined by the sponsor as a patient whose diary score at the 6-month and 12-month follow-up visit was 75 or less.

Next slide.

Clinical issues important to the FDA. The sponsor has anticipated the following physiological responses to the endometrial ablation procedure, one of which is pelvic cramping immediate post-procedure, and overall, pelvic cramping was reported by 94 percent of the UBT patients versus 84.1 percent of those patients who underwent the rollerball procedure.

A serosanguinous discharge was experienced during the 30-day post-procedure period by 74.6 percent of the UBT patients versus 65.9 percent of the rollerball patients.

Other anticipated physiological responses: nausea and/or vomiting during the immediate 24-hour post-procedure

period was reported by 23.9 percent of the UBT patients versus 16.7 percent of the rollerball patients.

For the primary endpoint, using the most recent data analysis that was submitted to the FDA on September 30, 1997, the sponsor has reported the preliminary success rate at 6 months for UBT as 78.9 percent for UBT compared to 85.7 percent for rollerball, and at 12 months the preliminary success rate for UBT was 81.6 percent versus 85.7 percent for rollerball. And Dr. Richard Kotz, who will be following me, will be giving a full statistical analysis of this data. So, therefore, based upon this data, as we heard earlier, the sponsor has concluded that both ThermaChoice uterine balloon therapy as well as the rollerball endometrial ablation achieved significant reductions in menstrual bleeding and significant improvements in quality of life.

Next slide.

In addition to Richard Kotz presenting the FDA statistical analysis, I'd also like the panel to note that in their panel package there is a clinical review by Dr. Gerald Shirk on this PMA, covering many of these issues, and also his clinical concerns.

I'd like to now highlight those areas of this premarket application which may prove helpful during the subsequent advisory panel discussion period.

Based upon the results of the pivotal trial, the sponsor has proposed the following indications for use statement for their medical device labeling, and that is, the ThermaChoice UBT is a treatment for excessive menstrual bleeding due to benign causes in women for whom childbearing is complete.

The sponsor has also proposed the following contraindications for use of the Gynecare ThermaChoice UBT System, and that is: a patient who is pregnant or wants to become pregnant in the future; a patient with a history of latex allergy or who has demonstrated a sensitivity to latex material; a patient with a known or suspected diagnosis of endometrial and/or cervical cancer or who has atypical endometrial hyperplasia; also, a patient with any anatomic or pathologic condition in which there is severe thinning or weakness of the myometrium; and a patient with active genital infection at the time of the procedure.

The sponsor has also proposed the following physician education binder which contains:

A review of both the international ThermaChoice UBT System clinical experience and a complete overview of the U.S. clinical data for the UBT system, and this includes the study methods, clinical trial design, inclusion criteria, patient pools, and the trial results, including

all key clinical measures and quality-of-life scores.

There is product information on the ThermaChoice UBT System. There are also clinical guidance modules which will be provided on patient selection, anesthesia regimens, pain management, and the role of UBT in the treatment of dysfunctional uterine bleeding. There is also an in-service video to provide the described product application, indications for use, patient selection, and directors for use.

There is a uterine model provided to the clinicians to demonstrate product use and to in-service clinicians on how to perform the UBT procedure.

Journal articles and abstracts relating to the ThermaChoice UBT System are also included. There's also a patient education brochure. This patient labeling can be used by the clinician to educate potential ThermaChoice UBT patients.

Next slide.

There are a number of clinical issues raised by the use of thermal endometrial ablation devices in general and the Gynecare ThermaChoice UBT System specifically. For example, what will be the long-term success rate for women with menorrhagia who have undergone thermal endometrial ablation? Also, what will be the long-term re-intervention

rate, that is, the rate of repeat endometrial ablation and/or hysterectomy, for women with menorrhagia who have undergone thermal endometrial ablation?

As we heard earlier from Colin Pollard, there is an FDA guidance document for thermal endometrial ablation devices that was reviewed by the Obstetrics and Gynecology Devices Advisory Panel in October of 1995 and finalized in March of 1996. In this guidance document, they've outlined a post-market strategy which may help to address these and other important clinical questions. This guidance document describes a follow-up plan where patients post-thermal endometrial ablation would be followed for a total of 3 years. That would include the 12-month follow-up period in the clinical trial as well as an additional 2 years post-approval. The emphasis of this follow-up would be on the need in these patients for either repeat endometrial ablation and/or hysterectomy.

The issue of unknown long-term effects of thermal endometrial ablation could also be addressed by this or other post-market strategies. This important question has been included as a discussion question to the panel.

At this point, I would like to introduce Richard Kotz, our FDA review team statistician, who will present his statistical analysis of the pivotal trial data. And I'd

like to hold any clinical questions that the panel may have until after his statistical presentation of the data.

Thank you.

MR. KOTZ: I will present the biostatistical review of Gynecare's clinical trial on endometrial ablation. I'm Richard Kotz of the Center's Division of Biostatistics.

First I'll review the study design and present the statistical methodology used to determine the sample size of the study. We will then look at patient enrollment. I will then discuss the effectiveness results, briefly discuss the complication rates, and present my conclusions.

This study is a controlled, randomized, two-arm clinical trial which compares Gynecare's uterine balloon therapy, which will be abbreviated at UBT in my slides, with a control, in this case rollerball therapy, which will be designated as RBT, and which is a recognized ablation treatment.

The sponsor chose as an endpoint a diary score of less than 75 for success. A diary score of more than 150 was required for enrollment in the trial.

Follow-ups were conducted at 6 and 12 months. The sponsor has also agreed, as you've heard, to conduct 2- and 3-year follow-ups in a post-market scenario as well.

In this study, 50 percent of the subjects were

less than 40 years of age and 50 percent were over 40 years. The study was randomized to ensure that it was split this way. As stated before, all women were required to be premenopausal.

The study was designed to test a comparison of two independent proportions. The null hypothesis is that the rate of success for balloon therapy and rollerball are equal, with an alternative that they are not equal. The expected success rate for rollerball was 85 percent. The clinical difference to be tested was 20 percent. Though this level may be considered high, it was considered acceptable to the expected safety profile and relative ease of use of the device when compared to rollerball, the control.

Based on a power of 90 percent and a Type I error of 5 percent, the calculated sample size per arm was 108. But with the sample size of 108 per arm and an observed success rate of 85 percent for rollerball, I want to make this point: It would require a success rate of 74 percent or better for balloon therapy to claim equivalence between the two devices using a significance level of 5 percent.

When looking at the comparison for each of the two stratum separately, the power is reduced to 65--for the stratum is reduced to 65 percent. There's a lot of details

on this slide, and I'm going to skip over it very quickly, but panel members can look at it more carefully in their leisure.

I'm going to briefly go through this patient tree. There were a total of 275 patients enrolled, with 137 receiving balloon therapy and 138 getting rollerball therapy. In the second--well, I want to point to the slide, but I guess I have to stay at the mike. Not all patients were anesthetized, and three patients were randomized to rollerball but received balloon therapy. Thus, 131 subjects were treated with balloon therapy and 124 with rollerball. Several were lost to follow-up and one to hysterectomy before the 6-month evaluation. Three more were lost to follow-up and three more to hysterectomy before the 12-month follow-up. The top part is the 6-month, and then move it up and you go to the 12-month.

As has been stated, at this time 85 percent of the follow-up has been analyzed. I believe the sponsor has--all patients have reached the 12-month follow-up at this point.

T2B

This is the success rate at 6 months. In parentheses are the sample sizes. When we look at the 6-month success rate, we find basically no difference in the overall rate for both stratum combined

. These results are in the bottom row, and you can see it's 78 versus 81 percent. But if we look at the top row, the under-40 age group, we notice that there might--we notice that it appears as if there might be a difference between the two groups. Though this difference is not statistically significant, this analysis is underpowered and the equivalence cannot be claimed with sufficient confidence. There is no difference for the over-40 as well.

Looking at the 12-month success rate, the results, which included at the time of reporting, as I said, 85 percent of the total number of subjects to be evaluated, we find these results to be consistent with those observed at the 6 months. No difference in the total, and, again, no statistical difference in the under-40 age group; again, it is underpowered.

In terms of complications, complications and adverse event rates, there was really not much difference between the devices, with the notable exception for post-ablation cramping. 16.4 percent of the balloon therapy patients experienced severe cramping versus 4 percent of the rollerball subjects. This resulted in a statistically significant difference at the p equals 0.001 level. But the sponsor claims this may be due to the different anesthesia regimens.

In conclusion, the study was well designed and conducted. We found balloon therapy to be statistically equivalent to rollerball with adequate power when both stratum were combined. Though balloon therapy was not statistically worse than rollerball for the under-40 age group, it should be emphasized the power of the test was only 65 percent. And, finally, we found more severe post-ablation cramping with balloon therapy than with rollerball.

I guess we're taking questions for both Dr. Harvey and my review.

CHAIRMAN EGLINTON: We're essentially at the point of break. Is there burning need to ask a small number of questions before we break right at this point? We obviously have plenty of time later.

Sentiment for break larger than for questions. Okay. So we'll break. We'll be back in 15 minutes.

[Recess.]

CHAIRMAN EGLINTON: Okay. Can we have any questions from panel members for the most recent team of FDA presenters? Dr. Perlmutter?

DR. PERLMUTTER: I have a question for Dr. Harvey. You mentioned that there was a 6 percent hysterectomy rate in the ablation group. When I read the PMA, they had put down several hysterectomies that were done for pain--I'm

sorry. That's not stated correctly. They had put down patients who had had decrease in menorrhagia as successes, but they had had hysterectomies later for pain. Was that part of your 6 percent?

DR. B. HARVEY: Actually, there are two parts to that. The 6 percent that I mentioned was actually during the international trial. The issue that you've just raised is actually something that the FDA and the company has discussed as far as when there is a hysterectomy that's done for pain, is that actually a failure? If the patient has had therapeutic success with a decrease in menses, with a diary score of less than 75, but is continuing to have pain, is that really a failure?

That's actually something that we have been discussing, and we have gone through all the different cases of hysterectomy and have tried to decide, based upon the information from the sponsor, on whether a hysterectomy is a failure in that specific case and whether the hysterectomy actually was a success. And part of what they mentioned, the sponsor mentioned, as far as adding two hysterectomies, one on the rollerball side and one on the UBT side, from drop to failure, is actually based upon the very point that you're making right now.

DR. PERLMUTTER: Thank you.

CHAIRMAN EGLINTON: Dr. Shirk?

DR. SHIRK: A question for Dr. Harvey. I've obviously had the privilege of looking at the statistics more significantly than the rest of the panel, but my question would be basically on the clinical analysis. Obviously you're looking at the overall stuff rather than total amenorrhea rates. Certainly the amenorrhea rate in the under-40 group from the balloon was significantly lower than the rollerball.

DR. B. HARVEY: I guess the 16 percent versus--

DR. SHIRK: And I guess a comment on breaking--you know, would it be important to break the statistics down as to total outcomes, you know, amenorrhea versus just light periods versus basically normal periods?

DR. B. HARVEY: I think you raise a very good point. If you're looking for an objective finding after a thermal endometrial ablation procedure, there's nothing much more objective than amenorrhea. The question is whether that is actually what the therapeutic desired result should be. If you have women with menorrhagia who are coming in and then go from a score of greater than 150 to a diary score of less than 75, you've actually returned them to a more normal period. So although they're not having--although they're still having a period, it's more in the

range of a normal monthly period, which, you know, there are issues as far as whether there actually are benefits to having monthly menstruation.

Is amenorrhea actually a desirable outcome, or are there benefits to losing blood every month? I mean, that's certainly an ongoing area of investigation as far as iron deficiency or blood loss and protective effects in other parts of the body. So I think it's an unanswered question. But you're right, a 16 percent rate of amenorrhea for a balloon is certainly much less than the success rate which they've talked about.

DR. SHIRK: Well, the only statistical significance that I would see would be that basically probably represents how much viable endometrium is still left, also how well interlinked pathology has been treated. If you look at especially Dr. Brooks' statistics--or studies before on underlying pathologies in these patients, a lot of them have adenomyosis. How deep do we need to get with the thermal thing? Does this represent an inadequate treatment, and are we going to see increased failures over time? Because certainly from our experience with hysteroscopic ablation most of the failures are going to come from that group of patients that continue to have a significant amount of flow. Even though initially you've adequately treated

them, over time they fail.

So the question would be: Is this a significant piece of data as far as long term?

DR. B. HARVEY: Well, I think you've raised a very good clinical point, and I think that the underlying premise is that that's something that needs to be addressed in longer-term follow-up. And that certainly, I'm sure, will come up in one of the panel discussion questions as far as the post-market strategy and length of follow-up.

MS. YOUNG: I have a question for John Murray. You posed a question at the end of your presentation with respect to the fact that the visual display does not show the actual therapy time. And I would like to ask if you could perhaps go into some detail about the feasibility of introducing the possibility of a visual display for the actual therapy time, because it seems to me that it would be very important for the clinician operator to, in fact, be able to, as he or she is proceeding, perhaps to be able to see how much time has elapsed since the actual beginning of the therapy itself. Especially if for some reason it's necessary to stop the therapy for any reason, then it would seem to me that the clinician operator would have to do some sort of calculation to know how much time has elapsed for the warm-up period and how much time has elapsed for the

therapy. And is it feasible to introduce a visual display of the actual therapy time?

MR. MURRAY: Well, I have an opinion about that, but I think I'd rather--there's a gentleman here I just met from Gynecare who probably can answer that question better, since he owns the device. Can I ask him to come up here and answer the question?

The question is: Can you reset the timer when therapy begins and have an accurate indication of therapy time? My opinion is yes, but I'd like them to address that. But I remind you that it's a simple fix to go into the software and make it reset to zero. But there are a lot of other questions involved with, well, how will it affect the installed databases that are out there in Europe already? Are you going to go change all these devices at once or just the U.S. market or whatever? But it can be done, yes. How hard is it to do and how much does it cost?

DR. McCOLL: If I can just make a clarification on the question, the question is: The device itself doesn't specifically tell how much the therapy time is because there's a preheat time that's before the therapy time. So the numbers you see on the display are the preheat time and the display time. Okay.

I guess my first comment on that, just to

understand, is that typically the preheat time is relatively consistent among most of the treatments. It's about 45 seconds, more or less. There is some slight variation depending on the size and volume that it takes to heat that fluid. That's the first thing.

The second thing is, from a safety issue, I would emphasize that if for some reason the device did shut down or power was lost to the system, we have treated patients for 16 minutes and shown that the device is safe even in longer treatments because the curve flattens out over time. So that would be the two key issues I would say in the way the device is designed right now.

I might ask that Dr. Grainger just make a comment because I think he's been involved with some of the international data we've had with different people on the time system. I think you also had one in your own study that shut down.

DR. GRAINGER: My name is David Grainger, and I'm an associate professor at the University of Kansas, and I have no financial interest in the company.

CHAIRMAN EGLINTON: But the company did bring you here and pay your expenses?

DR. GRAINGER: I'm optimistic that they will.

[Laughter.]

DR. GRAINGER: I think it's an interesting question, and I would just reiterate what Milt said. This is a very--the preheat cycle is fairly consistent among patients, and it's very short. And I'll grant you that, you know, gynecologists may not be the best mathematicians in the world, but the math is pretty simple.

Secondly, from the European studies, even if the device would shut down and you weren't paying attention to what the time was when it stopped, from the studies done--let me back up. The safety studies that we did looking at the thermistors on the surface of the uterus measuring the temperatures on the serosa, that study was done in Europe also, and the patients were treated with back-to-back cycles. So they got a total of 16 minutes of therapy. They were treated; then they were immediately retreated.

As Milt mention, those temperature curves really flatten out and actually go down just a little bit over the course of a full 16 minutes of therapy. So even if you were not paying attention and didn't know where you were in the procedure--that would be ideal to know--you know, you would want to know where you were. But even if you retreated, from a safety standpoint there wouldn't appear to be any problems with that.

CHAIRMAN EGLINTON: Dr. Blanco?

DR. BLANCO: Let me rephrase the question and see if maybe this clarifies it for us.

What's the purpose of having a timer on the machine if it's not to time your time of therapy? Do you understand how I've rephrased it?

DR. GRAINGER: Not exactly.

DR. BLANCO: Well, why do you have a timer that ticks off time if it doesn't turn on for--if it doesn't do it to help you measure what your time period that you want to appropriately treat the patient? In other words, what you want to know is you want to treat them for 8 minutes; right?

DR. GRAINGER: Correct.

DR. BLANCO: You want to know you've done that at the right temperature. What's the purpose of the timer if it starts as soon as you turn on the machine or as soon as you preheat it, but it doesn't include--it includes extraneous time as opposed to--I mean, it would seem--and I think that's the reason you brought up the question. It would seem that what you want to know is you want to treat them for 8 minutes, no longer, no shorter, so you want a timer that turns on when the temperature is appropriate and tells you it's time to shut off when you've done your time. So what's the purpose of not having it done that way?

Does that clarify it?

DR. GRAINGER: Maybe. You are correct in the sense that the parameters, the device parameters are set, as we heard John Murray talk about, in the software. So indeed, you cannot really override the parameters. So the preheat--it gives you an idea of where you're at in the treatment cycle. You cannot treat longer than 8 minutes after you've achieved a temperature in the balloon.

So to a certain degree, I suppose one could argue that the clock timer is occupational therapy for the treating physician in the sense that it just lets you know where you're at in the treatment cycle. But it doesn't--it's not critical as far as any control--as any external controlling of the device by the physician. It's merely a timer that lets you know where you're at.

Does that answer your rephrased question?

CHAIRMAN EGLINTON: Dr. Maples, do you want to take another--

DR. MAPLES: My question is: Do you have an option to treat shorter than 8 minutes? Or if it stops prematurely at 4 minutes into the first cycle, can you go to the next cycle and only treat for 4 minutes? Or does it go for another 8?

DR. GRAINGER: You could stop therapy at 4

minutes. You can shut the machine off. There's also warning--I mean, there are also audible signals from the machine to let you know when the treatment cycle has begun, so that you can then glance--if you're, you know, talking to someone, then you can glance at the machine and note in your mind what the time is.

It's not a difficult thing, you know, to keep track of where you're at in the procedure.

CHAIRMAN EGLINTON: Could I ask, what is the maximum range of the preheat time?

DR. GRAINGER: I believe I--it's up to 4 minutes. If the volume of fluid--if the temperature of the fluid has not achieved 87 degrees by 4 minutes, then the machine shuts off.

CHAIRMAN EGLINTON: I guess I have the same confusion Dr. Blanco does. Who cares about the preheat? What the therapist cares about is the therapy time, so why on earth would it not display the therapy time? That's incomprehensible to me and apparently to everyone else who's trying to ask the question here.

DR. GRAINGER: Well, from using the device, it doesn't seem to be a big deal, but, I mean, I understand--I guess I understand. What you're saying is that the clock should not start until the appropriate temperature is--

CHAIRMAN EGLINTON: Or you should have two clocks if you feel compelled to have a preheat clock. I don't understand why you want a preheat clock, but if you do, you should have two clocks, or it should reset when the therapy starts. What if you have a software failure and it's running for 22 minutes? I suppose somebody ought to be able to figure that out, but it would be a lot easier to figure out if the clock displayed 22 minutes and you know that it started at 0 at the time of therapy.

Dr. McColl?

DR. McCOLL: Just two points, just to clarify it with Dr. Grainger. One is, as he mentioned, there is an audible beep at the time the procedure reaches the therapy cycle. So it's actually very simple to figure out how long the procedure has been done by the audible beep and noticing by subtraction how much time is available. So that's one point.

The second point is in regards to the question of being able to go on for 22 minutes. As Dr. Grainger said, the maximum amount of preheat time would be 4 minutes. Of course, there's probably some minimal amount of treatment going on during the pre-treatment cycle as it's ranging up toward that time period. But then there's no way the device could be functioning for more than 12 minutes in total

because that would be the maximum the device could be used, and you would see that on the screen itself.

CHAIRMAN EGLINTON: Dr. Blanco?

DR. BLANCO: So what you're saying is the device shuts off automatically at 12 minutes?

DR. McCOLL: Absolutely. That would be the maximum.

CHAIRMAN EGLINTON: Dr. Chatman?

DR. CHATMAN: I guess I had a question about the other issue involved here, and that's heat transfer across the uterus itself. I suppose that's important.

In the feasibility study, Dr. Grainger, there were 8 patients. I guess you and Dr. Steege did it. But I didn't see any place where there was a mention of the size of the uterus, and I imagine that that would be one of the primers in the amount of energy that's transferred across the uterine surface. Is there some information about that available to us? And along those lines, will there be any-- I guess this question isn't for you, but will there be any labeling having to do with that issue when the device is on the market? Obviously a uterus that's post-menopausal will presumably transfer heat faster than one that's pre-menopausal and bigger.

But the first question is, you know, did you do

this thermocouple study on uteri that were 16, 18 weeks size?

DR. GRAINGER: No. The inclusion and exclusion criteria for those patients in the IDE feasibility study were exactly the same as for the clinical trial. So they had to have a cavity between 4 and 10 centimeters. So these were--they had no submucous fibroids and--you know, it was the same group of patients.

CHAIRMAN EGLINTON: Dr. Perlmutter had a question.

DR. PERLMUTTER: Actually, my question got answered, but I do have another question. With a 4 centimeter uterus, I don't remember seeing anywhere in this mass of material the size of the uteri that got treated. How many uteri below 6 centimeters did you have? That's an awfully small uterus, and for a pre-menopausal woman--

DR. GRAINGER: Which study are you talking about? The clinical trial or the feasibility study?

DR. PERLMUTTER: The clinical trial. Four centimeters is a very tiny uterus for a pre-menopausal uterus, and from somebody who puts in lots of IUDs, that's sort of too small to put in an IUD. So if we're talking about a uterus that small, are you really up to the fundus when you've done your sounding? Or how many uteri did you have at that level? It just seems very small to me.

DR. GRAINGER: According to Laura, there were three patients in the study that had a uterus--.

[Pause.]

DR. GRAINGER: Six total under 6 centimeters and three that were just above 4 centimeters, I guess.

DR. BLANCO: This is from the clinical study, so the 200-plus?

DR. GRAINGER: That's correct.

DR. PERLMUTTER: Were they all in the UBT group or--

DR. GRAINGER: The mean range in the UBT group was 8.5 centimeters, plus or minus 1.3, and in the rollerball it was 8.6, plus or minus 1.2.

DR. PERLMUTTER: But the ones that were in the 4 to 6 centimeter range, were those in the rollerball or were those all in the UBT group?

DR. GRAINGER: They were in both.

DR. SHIRK: Can I make a comment?

CHAIRMAN EGLINTON: Dr. Shirk.

DR. SHIRK: When I was reviewing data, I asked the question that you asked. The company did send me some data and breaking it down into different sizes, but the lowest grouping that they had was 8 centimeters and below as the smallest uteri, which was about a quarter of their patients.

So that, you know, it doesn't sound like they really had very good data on small uteri. Again, my question and yours is basically saying, What about small uteri? The question being, too, basically that the balloon device extends out to 6 centimeters on the gauge, so you're not completely putting the balloon inside the uterine cavity. You know, does that increase the risk of perforation? And also the other question would be, What about the endocervical canal and damage into the endocervical canal?

One of the problems with hysteroscopic endometrial ablation is that treating down into the endocervical canal has been reported to create some problems or damage to the descending uterine artery and severe hemorrhage immediately post-op or about 10 days post-op because of thermal damage to the descending uterine arteries, which really only run about 5 millimeters below the endocervical area. So my question would be, you know, does this increase the risk of this type of problem, or does it increase the risk of cervical stenosis post-op?

DR. PERLMUTTER: I was even thinking about the uterus that's acutely anteverted or acutely retroverted. You go up to 4 centimeters, and you really haven't even treated the upper portion up in the fundus of the uterus, and that's where my concern would come, because the

experience with IUDs is that when you only get to 4 centimeters, most of the time it's because you're not up in the fundus.

CHAIRMAN EGLINTON: Could I ask one more question related to size as well? It is obviously less significant, less important than the discussion of uterine size, but patient size, since the definition of obese is a BMI of 29.0 or greater, the mean and the UBT was 219.1 and the mean and the rollerball was 28.2; what do we know about normal-or-smaller-sized women with this?

DR. GRAINGER: Well, from a theoretical perspective, one would expect that estrogen production would be higher in women who are more obese. So, in essence, the study from that perspective, although it was not a significant difference between those two groups, the study would be biased against rollerball because of the higher BMI. But I do not know that we know the answer to that.

CHAIRMAN EGLINTON: I was not contrasting 29.1 versus 28.2 but 29.1 versus the rest of the world and that is a pretty big person.

DR. GRAINGER: Not in the United States.

[Laughter.]

CHAIRMAN EGLINTON: Are there any other questions before we move on to Dr. Harvey?

DR. BLANCO: Gary, just one more question and it's not really a question, more of a statement. I think it has been brought out and I think it would be an interesting point to see not just what your means were in terms of the depth of the uterus, but really where your ranges were and what data you have.

I think that there has been some concern by the panel for the small uterus and it may be that if there is not a lot of data for what the instrument does in the small uterus that we need to get more information on that. So, it might be interesting for you all to try to pull that out.

DR. GRAINGER: We will have it for you in just a minute.

DR. BLANCO: Okay.

CHAIRMAN EGLINTON: Any other questions before Dr. Harvey?

[No response.]

CHAIRMAN EGLINTON: Dr. Brian Harvey will present the discussion questions.

DR. B. HARVEY: The discussion questions have been broken down into different sections including the safety and effectiveness, labeling issues, the physician training program and, at the end, the post-market study strategy.

The first question for the panel discussion.

There was no significant difference in the success rate, as defined by a diary score of less than or equal to 75, of the rollerball versus uterine balloon therapy in the greater than 40 age group and using the initial data presented to the FDA of 82.4 percent versus 85.2 percent, respectively, one-year follow-up data.

In the less than or equal to-40 age group, the success rate for rollerball was greater than that for UBT, 91.3 percent versus 79.6 percent, respectively. As we heard earlier from Richard Kotz, those are not statistically significant differences. The question is, is this a clinically meaningful difference and do these differences raise any concerns regarding the effectiveness of UBT in the less than or equal to-40 age group.

Question number two. The reported incidence of post-procedure severe cramping in UBT patients, N equals 22; 16.4 percent, is more frequent in rollerball patients than N equals 5 or 4 percent. The sponsor suggests that this may be due to differences in the anesthesia regimens. And as we remember, they had discussed the difference between general anesthesia, percentages and conscious sedation, local anesthesia. Could this difference in the severe cramping rate be device related? And does this difference in the incidence of severe cramping raise any safety concerns?

Question number three. Based on the efficacy and adverse event data, do you believe that UBT is safe and effective for the treatment of menorrhagia for women either less than the age of 40 or greater to or equal to the age of 40?

Going on to the labeling session. Question number four. Based on the data presented, does the proposed indications for use statement adequately define the appropriate population for use of UBT? And as we heard earlier, the proposed indications for use statement is that the ThermaChoice UBT is a treatment for excessive uterine bleeding due to benign causes in women for whom childbearing is complete.

As we had heard the clinical protocol required study subjects to be pre-menopausal. Based upon the data supporting this pre-market application, should the indications for uterine balloon therapy be limited to only those patients who are premenopausal women?

Question number five. Based upon the clinical data presented by the sponsor, should a recommendation be made in the labeling for both a lower and upper limit in uterine size for UBT for which UBT can be used.

Question number six. In the proposed contraindication section, is that appropriate and are there

any additional contraindications for use of this device?

And as presented earlier, the contraindications as proposed by the sponsor, is a patient who is pregnant or wants to become pregnant in the future; a patient with a history of latex allergy or who has a demonstrated sensitivity to latex material; a patient with a known or suspected diagnosis of endometrial and/or cervical cancer, or with a typical endometrial hyperplasia; a patient with any anatomic or pathologic condition in which severe thinning or weakness of the myometrium could exist; and a patient with active genital infection at the time of the procedure.

Question number seven. Should there be any modifications to the labeling regarding the risk of pregnancy following the endometrial ablation procedure?

Question number eight. Is the proposed PATIENT BROCHURE appropriate and are there any suggestions for additions or changes to the patient labeling as proposed by the sponsor?

Question number nine. Aside from any recommendations for the indication and contraindication sections, does the panel have any other suggestions for the patient labeling or the labeling, in general, for this medical device?

Question number ten. Under the physician training program, based upon your review of the efficacy and safety data, do you feel that a training program is necessary to instruct clinicians in the use of UBT; and, if so, is the sponsor's proposed physician training program adequate to address user-specific safety and effectiveness concerns?

Under the post-market study section, question number eleven. Under the current FDA guidance, which had been discussed earlier, patients are scheduled to be followed for a total of three years after the endometrial ablation procedure, which was the one year pre-market during the clinical trial and the two years post-approval. Is the sponsor's proposed follow-up plan adequate to address long-term safety and effectiveness issues?

And the final question, number twelve. Are there any other issues of safety or effectiveness not adequately addressed in the labeling which should be addressed?

CHAIRMAN EGLINTON: Okay. Dr. Elisa Harvey will now continue the presentation.

DR. E. HARVEY: In order to provide a framework for the panel during their deliberations we wanted to review some definitions that will be important for them while they are considering the device.

First of all, safety, the basis for it is valid

scientific evidence, and I will provide the definition for that shortly. The device should demonstrate probable benefits to--or the probable benefits to health should outweigh any possible risks under conditions of use. And the device should, an absence of unreasonable risk associated with use of the device should be demonstrated.

The definition of effectiveness under the law is that it should be, again, based on valid scientific evidence and that it should be demonstrated that there is reasonable assurance that a device is effective when, in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when labeled, will provide clinically significant results.

As Colin mentioned earlier, the definition of valid scientific evidence, as it pertains to the evaluation of these devices, is primarily well-controlled investigations, it may also consider partially controlled studies, studies in objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with the marketed device.

And, finally, at the end of your deliberations today, the panel will need to make a recommendation to FDA and the panel has three recommendation options. The first

is approval and approval means no attached conditions.

The second is approvable subject to specified conditions. And the panel should specify exactly what all those conditions are. Of note, prior to the vote all conditions should have been discussed by the panel and listed by the panel chair.

The third option is not approvable and there are five reasons that are specified for denial of approval. Three may apply to panel deliberations.

The three reasons relating to panel deliberations for a not approvable recommendation are: Safety, the data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the proposed labeling.

Effectiveness. Reasonable assurance has not been given that the device is effective under the conditions of use in the labeling.

And the third is that the labeling, based on a fair evaluation of all the material facts and your discussions, you believe the proposed labeling to be false or misleading.

So, that information should be kept in mind during the deliberations for the rest of the morning and into the afternoon before a recommendation is made by the panel.

CHAIRMAN EGLINTON: Before we begin to address the discussion questions, is there any additional input from the sponsor or from the audience?

MR. CORSON: I am Stephen Corson from Jefferson University and I am here with Valley Labs today. If the patient has a menorrhagia score which is of great magnitude, she probably has a lush endometrium. So, my question revolves around the D & C part of this. I would ask the question, what bore canula was used, what was the degree of suction? Because the instruments can vary tremendously, between an office unit and an operating unit with respect to how much suction or vacuum is created.

And finally, since this procedure was done without respect to cycle timing, how important is the D & C, do you believe, in the long-term results, so far as the degree of amenorrhea or oligomenorrhea, which is achieved?

CHAIRMAN EGLINTON: Dr. Loffer?

DR. LOFFER: There was no control over the section that was used to curet out the cavity. This study compared both arms using a suction technique. I think there is a point to be made that there could be more thickness to the endometrium with this, but I point out that no matter what pre-treatment is done, suction, dilation and curettage, endometrial suppression with medications, I think they are

going to apply equally to the two arms of the study. So, I would not expect to see any difference if D & C weren't done and, as an example, endometrial suppression were used.

CHAIRMAN EGLINTON: Dr. Perlmutter had a question.

DR. PERLMUTTER: Before we go on, my remembrance in reading this protocol is that the D & C or the suction was done immediately pre-treatment. I would assume, and this goes out into practice, that we will be doing our endometrial suction first, waiting for the results and then doing this procedure.

If you now have a thicker endometrium how is that going to affect therapy? Do we know?

DR. LOFFER: In the European study it did not appear to make any difference whether timing or curettage was done. You may choose to do a curettage to obtain a pathology for the pathologist, tissue for the pathologist, but I don't think that is a mandatory part of this procedure.

My suspicion is that when it becomes available and if and when it becomes available, that most physicians will probably pre-treat their patients for endometrial thinning just as they do now with most of the resection and rollerball techniques.

CHAIRMAN EGLINTON: Dr. McColl?

DR. McCOLL: Dr. Shirk, this is just a response to your question that you had mentioned about the difference in uterine size. I think it was your question to get a breakdown and if we did not analyze the data properly for you I apologize. We certainly can get more data for you.

The way we understand the question, this is in regards to uterine size and the difference between the uteri and breaking down into very small uteruses. We were asked to do some statistical analysis by FDA, one of their questions, to look at different uterine sizes to determine outcomes by them. And, unfortunately, because there were so few uteri in the under eight size we had to break down into four different categories of equal distribution.

It was about 25 percent of patients in each one of these groups. So, I am just presenting that data as it was an answer to the FDA. That's my only comment back at this point.

CHAIRMAN EGLINTON: Dr. Blanco?

DR. BLANCO: Yes. Let me follow-up on that.

I think it is important if we don't have a large amount of data in the small uteri, because of the design of the machine and the way it would be used, in looking in--and that's one of the questions in the indications--of whether we have enough data in the small uterus to really say that

that machine is safe and effective.

So, I think it is going to be important to break-out that less-than-8 number because and then a possible indication that may be required, if there is not a lot of, you know, 7-and-6-centimeter uteri that were utilized, there may be a requirement for an indication that only uteri between 8-and-10 be used as opposed to 6-and-10.

I think we really do need to look at that data to see how many patient were in that.

CHAIRMAN EGLINTON: Dr. McColl?

DR. McCOLL: To answer that question, I do have that information, it was supplied to me. We have had 9 patients in the IDE study who were treated that had less than 7 centimeters, and there were 6 patients in the rollerball group that had less than 7 centimeters.

DR. BLANCO: Well, I guess I would point out two things. Number one, it doesn't sound like too many folks that are under 8 centimeters need this procedure in either case, since you did not find very many or, at least, in this group and I am not so sure that those small numbers really allow us to say what the effectiveness or safety might be in a small uterus.

DR. SHIRK: One other comment and to bring up two issues on how this procedure is going to be used. And the

question basically is it always going to be used in patients that basically have significant abnormal uterine bleeding? Obviously it is going to be used as a cosmetic procedure whether we want it to be or not. Certainly a lot of those patients are going to be under that time frame. It is going to be used in mentally retarded patients that have, that you are wishing to control the amount of uterine bleeding for their own sanitary needs. Those patients, obviously, have very small uteri.

And, so, that it does become a significant issue as far as I am concerned.

DR. BLANCO: Well, I guess, let me address your comment in two ways, having been here this four years. I think our purpose here is to address the issue, if given under the appropriate indications, is the product safe and effective and the issue is it is up to us to determine whether sufficient data to say, well, a small uterus should not be indicated.

Whether other people will misuse this or other devices, unfortunately, that is a reality that, as physicians, we all know exists and we cannot control that. So, I would not damn a particular product simply because it might not be utilized in the right way by some people.

DR. SHIRK: I was not suggesting that.

DR. BLANCO: Okay.

DR. SHIRK: I was just suggesting that those are two groups where you may run into small uteri and that it becomes a significant problem.

CHAIRMAN EGLINTON: Dr. Downs?

DR. DOWNS: I would note that with a 94.9 percent effective, that is probably 16 out of 17.

CHAIRMAN EGLINTON: Dr. McColl?

Dr. McColl passes the baton to Dr. Loffer.

[Laughter.]

DR. LOFFER: There a couple of points that I would make. One, 25 percent of our patients with a success rate of 94.1 percent were in the 8 centimeters-group and less. Less than, I am sorry, less than 8 centimeters.

The other factor--I appreciate the concern for the creation of bleeding, but I think primarily those were in techniques where there was actually cutting into tissue as opposed to just thermal damage in the tissue. Now, that is one concern about being in the lower segment.

The second concern about being in the lower segment is creating an hematometra. In our series the only hematometra that was created was in the rollerball series, not in the ThermaChoice. And I think if you think about it, even if in a small uterus, the balloon is down in the endo-

cervix, the balloon does not get hot. You have to get some water down there to make the destruction occur. And even if you were to get some water down into a small crevice in that area it is not going to circulate very well. In reality I do not think you see water down in the lower segment.

So, I do not worry about that or see that as a concern for those reasons.

CHAIRMAN EGLINTON: All right, can we move on to the first question, the discussion questions?

Safety and effectiveness. While Dr. Harvey is getting those questions up on the board, could I suggest or could I ask, what was the reason for the age-40-under-over, where did that come from?

I mean who interjected the 40, who introduced the 40?

DR. BLANCO: I think the issue you are probably asking is, the original study was designed to take premenopausal and that is what the number that was arrived at for achieving power. And now we have subdivided the study, not to its original intent, into over-and-under 40 and have a major question about it. And now you are saying, well, who decided to look at it under 40 and above 40, is that what you are saying?

CHAIRMAN EGLINTON: Right. I could describe as

Colin is coming to help me. Dr. Heinz Miranda, the Chief of the Division of Epidemiology and Biostatistics at NICHD, calls that salami slicing. The power calculation was performed, the study was appropriately designed and carried out and then, after the fact, all of us in clinical practice start salami slicing the outcome data into smaller and smaller sub-categories. And we have been through that, Lord help us, with the home uterine activity monitoring.

[Laughter.]

CHAIRMAN EGLINTON: And I was just wondering if there was some power physiologic justification for doing it here? And I do more OB than GYN but I was not aware that age 40 was really significant other than that was the first time that I recelebrated an anniversary of my 39th birthday.

[Laughter.]

MR. POLLARD: I think you will find the answer is somewhere in between the salami slicing and study design. When we worked with the company on their study design, we defined the population to be premenopausal but we wanted to be sure that we would, in fact, get some younger women in that group.

And, so, the stratification took place, as I understand--maybe somebody will correct me if I am wrong--took place before randomization to be sure that there will

be an equal number in each group. But the power of the study and the study numbers were designed for an overall power.

So, you only are going to have power for the overall group but we wanted to ensure an equal split between the two so that is why, as Mr. Cox pointed out, you really have only 65 percent power to look at the less than 40 and greater than 40. It was essentially a compromise kind of a situation.

CHAIRMAN EGLINTON: Dr. Shirk, would you care to comment about 40, over or under?

DR. SHIRK: Well, I think it is significant and it is nice to have it for one reason and that basically, first of all, a group over 40, when we look at long-term success rates, is going to be significant because nature is going to add to their success rate significantly in that group and a significant number of those patients are going to go into their menopause during their follow-up time frame, so, that solves the problem anyhow. So, the under-40 range is going to be more significant in the long-term follow-up, I would think.

Also, I think there is some suggestion from hysteroscopic studies that younger patient's success as far as the procedure over time is less than the over-40 patients

who are making less estrogen. So, I think there is a reason to have the breakdown.

DR. BLANCO: One of the things that concerns me and it was brought up, was the gentleman who brought up the issue of the curettage and why the curettage was done ahead of time. Because it may not be an issue of age at all. It may be an issue of thickness of the endometrium, as you pointed out.

With possibly higher levels of estrogen in the younger women you may be dealing, what we may be seeing is not necessarily an age effect but it may be an endometrial thickness effect. Now, I do not know if there was any measurement or any attempt to look at endometrial thickness in the study and see whether success correlated with that or not, but I would, that is one of the ways that I sort of look at what we may be seeing in this over-and-under-40 group.

CHAIRMAN EGLINTON: Ms. Domecus?

MS. DOMECUS: I wanted to make two comments on this. One, if you look at just the PMA subject device, it performed basically equally well in younger patients and older patients and I think that is important to know.

And second, if the sponsor was going for a claim based on this data the FDA would never allow it because the

results are not statistically significant and the power of the analysis is also insufficient. So, I do not think in reverse this data should be held against the manufacturer.

CHAIRMAN EGLINTON: Does anyone on the panel feel that the data are compelling, that there is some reason to change the labeling or something relating to a woman's age? Is there anybody on the panel bothered by this small discrepancy for under-40/over-40?

[No response.]

CHAIRMAN EGLINTON: The answer to the question, I think, then is does this difference raise any concerns regarding the effectiveness of UBT in the less-than-or-equal-to age 40? I mean we have discussed it, but does anybody have any significant heartburn over that?

[No response.]

CHAIRMAN EGLINTON: No objections if we move on to question two.

Okay. The reported incidence of post-procedure cramping in UBT patients, 16.4 percent greater than RB. The sponsor suggests this difference may be due to differences in anesthesia. Is this difference device related? Does this difference in the incidence raise any safety concerns?

First, does anybody have any feelings about device-related versus anesthesia-related or do we have any

way to sort that out?

DR. MAPLES: That is my question, how do you sort that out?

DR. BLANCO: Well, the question is they should have that data. I mean they should not imply--I mean you should know which patients complain of cramping, severe cramping and you should know which patients got what anesthesia. So, I think you ought to just present us the data. I mean you should not imply it. You should either have the data or not have the data.

CHAIRMAN EGLINTON: So, that is perhaps something the company can look up at lunchtime. You had not planned on eating during lunchtime, had you?

[Laughter.]

CHAIRMAN EGLINTON: You can dredge that out of your notebooks, please, at lunchtime and then show us that.

DR. MAPLES: Also, the implication was that this did not have any clinical significance. Does that mean that none of these patients required any further treatment or do you have the numbers of how many patients required for the treatment for the severe cramping and what treatment did they need?

CHAIRMAN EGLINTON: So, this is more information you can pick up at lunchtime, how many patients required IV,

PCA; how many patients required motrin?

MS. PENDLEY: Laura Pendley with Gynecare, we will do that right after lunch. We have all of that data available.

CHAIRMAN EGLINTON: Perfect.

Dr. Shirk, do you have--

DR. SHIRK: I guess my only question about this whole anesthetic question is basically if you have got more cramping with the uterine balloon, post-op, why do you not have equal or more cramping with the rollerball and why were the statistics different between the anesthetic use other than operator choice?

And the idea that the operator was trying to prove that you could do the procedure under local anesthesia rather than a general anesthetic, whereas with rollerball they are more comfortable with simply putting the patient to sleep or giving them a spinal block to achieve anesthesia. So, it would seem the amount of pain involved both ways would be equal.

Certainly I would wonder how one could do three minute D & C under local anesthesia. I have a hard time with patients enjoying an endometrial biopsy, under paracervical block alone, doing a full three minute D & C.

DR. STEEGE: I am John Steege from the University

of North Carolina and I also hope that my expenses will be paid. Having done the balloon one or two times, it became readily apparent that the stimulus to the patient was far less than that of a hysteroscopy. And it became readily apparent that a paracervical block with a bit of IV sedation was perfectly adequate.

We also understood that pre-medication with NSAIDs was very effective at reducing both the pain of the procedure and any cramping thereafter. So, that is why the drift went towards local anesthetic procedures.

Regarding the suction curettage, the reason why that was included in the protocol it was my understanding that, in fact, to make the rollerball portion of the procedure easier and those of us who are rollerballers appropriate that that does make that procedure quicker to do and probably more complete.

That is why it was made the same in both arms.

CHAIRMAN EGLINTON: Thank you.

Any comment on does this difference relate in any way to safety concerns? Does it raise safety concerns in anyone's mind?

Dr. Perlmutter?

DR. PERLMUTTER: I would like to ask another question. In the protocol it stated that with the UBT

therapy that the patients had profuse discharge several weeks after the procedure and they did not see that with the rollerball. Did I read that incorrectly or is there a difference in what happens afterwards?

CHAIRMAN EGLINTON: David Grainger.

DR. GRAINGER: There may be. Conceptually and one of the parts of this question is, is that could the difference be device-related? I think we have to say, at least for myself, that it might be. The way that I look at this and those of us who do endometrial ablations know that as we do that ablation there is a continuous flow of fluid through the uterus. So, as we are destroying the tissue, ablating it with whatever technique that tissue is removed through continuous flow. As opposed to creating a burn, a global burn, if you will, that then over time will slough.

I think that might also be related to the cramping because you have, I think there may be a more profound release of prostiglandins from this tissue. And I can tell you, and after lunch we will look at the 13 patients, almost none of them received pre-operative non-steroidals. So, all of them were under-dosed from the prostaglandin inhibition point of view. So, that is my take on the cramping issue.

DR. PERLMUTTER: That actually makes more sense because if you think of it the paracervical block should

have given them more comfort than general anesthesia.

DR. GRAINGER: Right.

DR. PERLMUTTER: And, so, to have more cramping in this group, at least in my head, does not compute. So, that makes more sense.

CHAIRMAN EGLINTON: Any other comments on the cramping?

[No response.]

CHAIRMAN EGLINTON: So, we will have a little bit more information about anesthesia pre-during-post, after lunch and will hopefully address some of the concerns about operator bias. Because obviously there was some bias introduced here, natural enough, but we just need to hear about it.

Dr. Chatman?

DR. CHATMAN: I just wondered if it were possible that the distension of the uterus for the balloon could cause the cramping, is that possible?

DR. GRAINGER: Actually it is not, in patients that are just under paracervical it is not the distension of the uterus that causes the discomfort. They tolerate that quite well. But it is the heat. You know, once you turn the heater on that is what causes the cramping.

So, to answer your question, no, it is not the

distension, it is really the heat.

CHAIRMAN EGLINTON: Dr. Blanco?

DR. BLANCO: You brought up the issue of nonsteroidal anti-inflammatories as that they may also have an effect in dealing with this cramping. So, if the data for that is available for those patients that complain of excess cramping it might also be interesting to look at in terms of making some sort of decision about this excess cramping issue.

CHAIRMAN EGLINTON: I am not sure that we can really get to question three. It looks like kind of the end of the day. That based on efficacy and adverse events, do you believe it is safe and effective? That is kind of the ultimate question, is it not? I mean that is what we have to vote on at the end of the day. So, we will skip question three.

Can we attack one more of these at least before lunch and I would go to labeling. Based on the data presented--it is a little bit of a grammatical problem here, is it not--does the proposed indication statement. I guess it is a statement, okay. Does the proposed statement adequately define the appropriate population for use of UBT? It is a treatment for excessive uterine bleeding due to benign causes in women for whom childbearing is complete.

The clinical protocol required study subjects to be premenopausal. Based upon the data supporting this, should the indication for uterine balloon therapy be limited to premenopausal women?

Dr. Shirk, do you have a comment?

DR. SHIRK: Well, just that obviously we do not have any data on the post-menopausal patient. And, so, the question is, you know, without studies and efficacy in those patients, how should we proceed? And by that, I mean that if you look at the hysteroscopic data on patients who are post-menopausal, obviously the success rate is much higher than premenopausal women.

The use in this situation obviously involves women who basically would be using hormone replacement therapy, generally the combination therapy and that 30 percent who continue to bleed on the combination therapy who want to continue and do not want to have cycles and, so, therefore the procedure is used to maintain those patients on hormone replacement therapy.

And the answer is we really do not have any data as to the efficacy of the procedure in this group. Are they going to have the same success rate that the hysteroscope endometrial ablation patients have? Most of those have about a 90 percent amenorrhea rate. And certainly

amenorrhea becomes a much more critical issue in this group because, obviously, what you are trying to do is stop these patients from bleeding at all.

And, so, I think the indications in use in this whole group changes. And at this point, we certainly do not have any data, although this is probably, if we do not provide anything on the labeling, at least, or look at the studies, basically we are certainly going to see a major use for this. This is certainly going to be one of the major uses of the device.

CHAIRMAN EGLINTON: Dr. Blanco?

DR. BLANCO: Well, you know, I am worried about what you say because I do not think we have any data that has been presented on post-menopausal women. Plus, I think that post-menopa--menorrhagia in a post-menopausal woman has a much more severe or could potentially have a much more severe cause in terms of ovarian malignancy, hormone producing malignancies, malignancies on the endometrium, itself.

So, I really would be concerned about approval for anything other than pre-menopausal women at this point, unless, you know, some data on post-menopausal women were to be put forth.

CHAIRMAN EGLINTON: Dr. Chatman?

DR. CHATMAN: We do not make that distinction in other forms of ablation, so, I am not sure if it is appropriate here.

CHAIRMAN EGLINTON: I think the issue really is, as Dr. Blanco said and as Dr. Shirk said, we just do not have the data because the protocol applied only to premenopausal women.

MS. DOMECUS: Maybe instead of restricting the indication statement there could be just a statement somewhere else in the labeling under a different section calling the reader's attention to the fact that the clinical data is just on premenopausal women.

DR. BLANCO: I do not think I buy that one. I really think that, and I would like to hear from the OBGYNs that did some of these studies but I would like to hear them--I think there is a difference and I think we do make a difference. I think in a woman who bleeds below a certain age we are not thinking of endometrial cancer so we are less likely to do sampling and more likely to use medical therapy. Whereas in a older, post-menopausal woman, if you have bleeding, what is the first thing you are going to do? You are going to sample the endometrium to see what is going on.

So, I think there is reason in terms of management

of the patient as to why a post-menopausal woman would be different in terms of much higher risk that you are not dealing with a benign procedure. And this is easy enough that it can be done. I mean, obviously, it is going to be an easy procedure to do and I would be concerned that people who have got malignant conditions would have this applied to them in a postmenopausal age group. I would like to see some data.

CHAIRMAN EGLINTON: I think, as Dr. Shirk has said, once a technology is released, it is going to be applied by many people for many other uses. Other than the labeling, I think our task is to make sure the labeling reflects the data presented in the PMA which is premenopausal.

Dr. McColl?

DR. STEEGE: John Steege again. A fundamental tenet of gynecology is if you have postmenopausal bleeding, you sample the endometrium, and I do not know that I see a great hazard in this being--I see the problem is possibly some less efficacy. I do not see it as a safety issue. Because if you are, indeed, sampling in the endometrium, I do not think that should be any more prone to error in a person who is a ballooner versus a person who is a rollerballer.

DR. MAPLES: In terms of the size of the endometrial cavity, did you have a problem at all with the postmenopausal uterus, do you think there would be an issue?

DR. STEEGE: Certainly the sampling of the uterus should involve sampling of the depth as well. And if we agree upon some number below which the balloon should not be used, then that would provide sufficient information to allow selection of patients postmenopausally. Many people who are postmenopausal and are on continuous hormone replacement will maintain their uterine size. So, I think that is a decision of the Committee to set a size limit and suggest appropriate measurement as one would do any time you do an endometrial sampling.

DR. BLANCO: I want to make sure we are clear. Do we have any data on any postmenopausal women that have used or where this instrument has been used on them?

DR. MAPLES: No. No.

DR. McCOLL: No.

CHAIRMAN EGLINTON: Maybe we can edit that question in the PMA.

DR. BLANCO: Yes. So, there is no data on postmenopausal women. I think the indication has to be what the data shows.

CHAIRMAN EGLINTON: Any other comment on that

point, premenopausal, post-menopausal?

[No response.]

CHAIRMAN EGLINTON: We are going to have, after lunch, some more data on sizes of uteri and we will have stratification, 4, 5, 6, 7 centimeters. And we will have more information on anesthesia.

So, maybe now is a good time to take our scheduled break. We will be back at 1 o'clock.

[Whereupon, a lunch recess was taken at 11:58 a.m.]

[A F T E R N O O N S E S S I O N]

[On at 1:02 p.m.]

CHAIRMAN EGLINTON: Okay, let's all get started.

DR. E. HARVEY: We need to take a few minutes to go over tentative 1998 panel meeting dates. So, if the panel members could pull out their calendars, if they have them. This may not pertain to everybody at the panel meeting today because some of us are just temporary voting members. You know who you are.

CHAIRMAN EGLINTON: But there is one very significant question, the answer to which, we need to seek within the audience.

DR. E. HARVEY: Someone must know this. When is Superbowl Sunday?

CHAIRMAN EGLINTON: The date of Superbowl Sunday?

[Laughter.]

CHAIRMAN EGLINTON: Who knows when the Superbowl is?

[Simultaneous conversation.]

DR. E. HARVEY: Generally speaking, we try to schedule four meeting dates a year and we try to space them roughly evenly-spaced, and we've in the past tried to go for January, April, July and October. I am proposing that we try to schedule a meeting in January for the 20th and 21st

of January which are a Tuesday and Wednesday, because the Monday is a holiday.

CHAIRMAN EGLINTON: Dr. Blanco?

DR. BLANCO: I am only, since I am an out-going panel member, I am only good for January and that is a bad weekend for me, again.

DR. B. HARVEY: The following weekend is Superbowl activities.

That leaves either the first weekend or the last weekend in January. I will mark down the 27th and 28th in January. The next date will be in April, let's go for a Monday, Tuesday. I am going to mark down the 6th and 7th of April.

We next need a weekend in July. So, the 20th and 21st of July. And then a weekend in October, let's try for the 19th or 20th.

So, for the record, the tentative meeting dates for this panel for 1998 are Tuesday and Wednesday, January 27th and 28th; Monday and Tuesday, April 6th and 7th; Monday and Tuesday, July 20th and 21st; and Monday and Tuesday, October 19th and 20th.

Okay, I think we can move on.

CHAIRMAN EGLINTON: Okay. The sponsor had some homework to do at lunchtime. Do we have some more data?

DR. McCOLL: Milton McColl with Gynecare. Just one comment before we start that discussion. During the discussion we had during the break, we are very sensitive to some of the discussions that came out earlier about post-menopausal women and realized that in the IDE study, as discussed, there were no patients that were treated that were post-menopausal women.

So, one thing we would like to suggest or would certainly support on the company side is an addition made to the indications for use, statement read that the word, post-menopausal women should be in there. Excuse me, pre-menopausal would be inserted here.

So, the statement would now read: The ThermaChoice Uterine Balloon therapy system is a treatment for excessive menstrual bleeding due to benign causes in pre-menopausal women for whom childbearing is complete.

CHAIRMAN EGLINTON: Thank you.

DR. McCOLL: Dr. Spirtos will come up and answer some of the additional data you asked for.

DR. SPIRTOS: I am Doctor Tanya Spirtos and I am a clinical instructor at the Stanford University School of Medicine. I have no financial interest in the company and I hope my expenses will be paid. The first bit of homework was on the uterine balloon therapy patients with complaints

of severe cramping during the first 48 hours after treatment.

There are here 13 patients. Pre-operatively the nonsteroidal anti-inflammatory drugs which were used in only about half the patients were not used in what is recommended as therapeutic levels in the PDR. These patients had a variety of different types of anesthesia, bearing from PCB, which is paracervical block, general anesthesia, intravenous sedation, or GA, which is also general anesthesia.

Post-operatively these patients received narcotics. Now, I want to mention that when we are talking about narcotic doses, we are talking about a single injection of perhaps Fentanyl or Morphine in the recovery room. Each one of these patients, as well as the rest of the uterine balloon therapy patients and rollerball patients went home during the standard two-hour post-operative recovery period. None of these patients were seen back in either the emergency room, the doctor's office or the surgi-center for additional medication.

When these patients were sent home with post-operative pain meds, whether they were NSAIDs or narcotics, the narcotics would be Tylenol Number 3 or Vicodin. And these patients would typically use one or two tablets.

In retrospect, with 20-20 hindsight, I think that

in my own patient population I would, in the future, I would be more consistent with pre-operative nonsteroidal anti-inflammatory drugs as soon as the patient came into the pre-op area and I would consistently caution the patient to take something that evening when she got home and perhaps again at bedtime, so, that she would be less uncomfortable.

Most of the patients that I talked to a week later had no memory of this type of cramping. So, whether the care coordinator commented on it in the recovery room or the clinical coordinator talked to her in 48 hours and it was mentioned on the phone, the patient did not complain of it, one week later when I saw her.

This is obviously not a safety issue. None of these patients had complications or adverse effects. If anything, this is educational for us, so that we change the way we pre-treat these patients and the medications we give them postoperatively.

Now, the second bit of homework that I did--

DR. BLANCO: Before you go on?

DR. SPIRTOS: Yes?

DR. BLANCO: Refresh my memory again, specifically how you arrived at that there were severe or that there were cramping in this group, how did you gather the data and when was it that this complaint was made; refresh my memory.

DR. SPIRTOS: These complaints were culled in several different ways. One was the clinical coordinator observing the patient in the recovery room and making a note of none, mild, moderate or severe cramping.

The second was the postoperative phone call that the patient received two days later at which she would be asked the same type of question: Did you have any and they would ask, well, was it mild, moderate or severe? And, typically we would say, well, how many or did you take any medication and they would say one or two. And then I would ask again at the 7-day visit, did you have any discharge, did you have any cramping, did you have any fever?

DR. BLANCO: Okay. And did I understand you correctly that at the 7-day visit the patient did not remember that, so, does that mean--when did the cramping--in other words, when did these patients complain about the cramping or were noticed to have the cramping? Was it immediately post-procedure in the recovery room, during the next day call or in the 7-day?

DR. SPIRTOS: It was within the first 48 hours and it was, some were in the recovery room, some were in that first evening, typically.

The second piece of homework was about uterine size. And as obstetricians/gynecologists we are very

familiar with uterine size and what we are talking about. For the people who are not familiar with this I wanted to clarify something.

When we talk about the size of the uterus on a pelvic exam, we are feeling from the top of the fundus to the cervix and we typically say 6 centimeters, 7 centimeters. For this study we are measuring the inside of the uterus from the tip of the endometrial cavity the external cervical os. And during this procedure we were able to measure that three different times, well, four different times.

Preoperatively, when we assess the patient, we would do an endometrial biopsy in the office and we would make a note on the Pipelle how far it was inserted.

In the operating room, we would sound the uterus and make a note. We would do the suction curettage and we would look at the canula when we were done to see how bloody it was and then we would insert the uterine balloon catheter.

Obviously if our evaluations had shown that the uterine sounded 6 or 7 centimeters, and then we only inserted the balloon 3 centimeters, we would realize that there was a little bit of a discrepancy and we really weren't into the uterine cavity. So, I think that address

the question Dr. Perlmutter brought up earlier as to how do we know whether or not we are just in the canal as opposed to in the uterus.

Looking at the number of patients, there were 15 patients altogether that sounded less than 7 centimeters. So, this is 6 percent of the total population. There were 9 in the UBT group of which these were equally split between success and failure, there were 6 in the rollerball group equally split, there were no complications and the single case of hematometra was not in this group of patients.

So, this appears to be equal efficacy. This is not a safety issue.

DR. BLANCO: Well, I just would point out to you kind of an interesting issue. There are 15 patients in less than 7 centimeters and you have a failure rate on 7 of them, which is little under 50 percent which is significantly different than the rest of your population.

DR. SPIRTOS: But it is also that way in the rollerball group.

DR. BLANCO: No, no, I'm not trying to differentiate between the two. I will tell you that 9 and 6 is too little for me, okay, in the less than 7 centimeters, right off the bat. But I also find it interesting that in the small uterus neither of the techniques seem to work

anywhere near as well as they seem to work in the larger uteri which is an interesting finding.

PRESIDENT WOLFENSOHN: Dr. McColl or Dr. Spirtos, can you tell us, do you have, how many patients are there from 7 to 8? Over 7 but under 8 centimeters?

DR. McCOLL: We will have to look at that data in just a second. We know that the 8-and less was a quarter of the patients, so, that is a good estimate of what it is, whatever it is minus. So, it would be about 30 or 35 patients, relatively, minus 9. That's my estimate and we can look it up exactly.

DR. SHIRK: Since ultrasound was part of the criteria or at least one of the ways of evaluating the uterine cavity, was any attempt made to look at the size of the cavities from an ultrasonic standpoint?

DR. SPIRTOS: Well, that's an interesting question. Because I, personally, found that very interesting and I did it in my patients. I would routinely measure on ultrasound at the same time I was assessing the uterus for fibroids and the ovaries for cyst, I would measure from the tip of the cavity to the internal os and then correlate it with what I got later on sounding it. So, I have an interest in ultrasound and I am lucky in that I have a machine in my office that I can use it at the flip of

a switch. And there was no discrepancy really between what I measured and what I later saw in the operating room.

One other piece of information the question arose also as to the heater element within the balloon catheter and it is of interest that the heater occupies the top 2.2 centimeters of the balloon catheter. So, that in our patients who are sounding less than 7 centimeters the heater is definitely within the endometrial cavity. Our patients would have to be minuscule uteruses in order to not fit within the cavity.

DR. BLANCO: No, it's not an issue. And as you pointed out the rate is not different for this small number of patients but I mean it is sort of interesting that neither procedure seems to have anywhere near as good a success rate when you have got the small uterus. And I don't have an explanation for it, I'm just making that observation.

DR. SPIRTOS: Some other type of problem going on in the patients?

PRESIDENT WOLFENSOHN: Dr. McColl?

DR. McCOLL: Here again, I would just like to caution us about the salami slicing of the data. This is a very small number of patients to be able to make a--and I think you used the word, significantly less effective, and I

think I would just be careful, at least that is what is quoted here, be careful of making numbers from the data, very small numbers, as we said, of slicing the data in that direction. I just wasn't sure if you could see the data from your angle. It said, 5 and 4, and 3 and 3, if you weren't able to see those numbers.

DR. BLANCO: Seven out of 15.

PRESIDENT WOLFENSOHN: Any other questions or comments from the panel members on the issue of the anesthesia differences, the cramping?

[No response.]

PRESIDENT WOLFENSOHN: Any other question?

I think the question we are presented with is, could this difference be device related? Does anyone have any concern about safety with regard to the difference in cramping? Is everybody satisfied that this has something to do with the anesthesia or does anybody care?

DR. BLANCO: Well, I don't think they have shown, if you looked at the numbers they have put up, they didn't divide it up, but it looked like half of the patients got general and the other half did not; they got other things. We can re-check it if you want by putting your handwritten data on that had the non-steroidals. But it looked like half the patients that complained of cramps received general

and the other half had not?

So, I don't think you can ascribe to anesthesia, I don't think it is an issue of safety but I think it may be an issue of labeling as a side effect that, you know, you have a higher rate.

DR. SPIRTOS: Basically when you look at all of the anesthesia types that were used in our patients, the balloon patients had 53 percent general and the rest were split between intravenous sedation and paracervical as well as an occasional regional block. So, that is very similar to the pattern that we saw in patients with severe cramping. Half of those had general anesthesia and the other half had a combination of various other agents.

DR. BLANCO: Exactly and that's my point. I don't see how you can ascribe it to anesthesia because--

DR. SPIRTOS: No. I think that was merely one variable. I think that because of the way the device works and the heat that is generated globally, that there may be a release of prostaglandin that we are not seeing in our rollerball patients. And if we pre-treat the patients with not enough nonsteroidals anti-inflammatories, give only half of them adequate anesthesia and then we are chincy with the post-operative medications, we are going to end up with severe cramping. Overall the patients are just as satisfied

but I think the nursing staff would prefer that we have adequate pain control.

DR. BLANCO: Okay. You're presuming in your statement that you just made, two things. One, you were chincy in your nonsteroidals and on your post-op and you don't have the data to prove that. The data that you have is that the group of patients that received the balloon had a higher rate of complaining either to the case manager or to someone that they had cramps in the first 48 hours.

I don't think you know why that is. You have a theory that it is the prostiglandins and I think you can go back out and say if you had sufficient nonsteroidals that would block it. But at this point, from the data you are presenting, I would say you have got a side effect that you need to label and that you need to know; that you have a higher rate from your own data.

I don't mean to belabor this point, Mr. Chairman, if you think I'm overdoing it here let me know.

DR. SPIRTOS: Just one portion of what you asked about, the anesthesia, when you look at general anesthesia and severe, there was twice as much severe cramping in those patients who did not get general anesthesia. So that is one of the variables.

You know, we have looked at the combinations of

medications that were given to the patients and there are so many combinations and doses that it would be very difficult to make any generalized statement about what the causes or what could be implied. But basically--

DR. BLANCO: That's the point I'm trying to make. But am I reading your data incorrectly that your balloon therapy group had a higher rate of complaining of cramping than your rollerball?

DR. SPIRTOS: It had a higher rate of observed complaints or verbalized complaints--

DR. BLANCO: However you want to word it.

DR. SPIRTOS: --which were not safety related. Yes.

DR. BLANCO: And you have theories but you don't have a clear explanation, that's fine.

DR. SPIRTOS: We have theories and since there are no good long-term studies that can elucidate where this is coming from all we can try to do is preemptively treat it in the future.

DR. BLANCO: Well, you could study in the future and answer the question whether you would prevent it from nonsteroidals. And the only point I'm making is that not that this means that you cannot use it but I think you do have to label it because I think you have a significant

complication that occurs more often in one group than the other.

I will get off of that.

PRESIDENT WOLFENSOHN: Are you concerned about safety, Dr. Blanco?

DR. BLANCO: No, I'm concerned about labeling. My issue is not safety at all. My issue is this is not going to block, you know, my view of the procedure. What I'm saying is if they don't have an explanation then I think we need to say in the findings, this happened, it was mild, didn't seem to bother anybody and at the end everybody was satisfied with it, all the patients. But you might expect that. I think you owe the patients the expectation that you may wake up and you may have a lot of cramping and they need to know that, that's all.

PRESIDENT WOLFENSOHN: But it's not a safety issue.

How about, can somebody just tell me quickly or in the next few minutes, over 7 centimeters number of success, number of fail, while we are going on here?

I have under 7 centimeters. I know that is 8 and 7. Can you give me the numbers for over 7.

DR. McCOLL: We don't have it broken down.

PRESIDENT WOLFENSOHN: Can somebody add it up so

that we don't have to add it up?

DR. McCOLL: I don't know if this addresses your question. This is Dr. McColl again.

PRESIDENT WOLFENSOHN: I'm looking to fill in. I have a 2 X 2 contingency table in Microsoft Excel with two boxes filled in and I'm trying to fill in the other two boxes.

DR. BLANCO: We will see if we can break that down for you while the discussions are going on.

PRESIDENT WOLFENSOHN: Dr. Harvey is wending his way to the microphone.

DR. B. HARVEY: Actually I didn't know if it would be helpful if we just gave a little background into some of the discussions that the reviewers were having as far as the whole issue of cramping. Breaking it down to severe cramping, moderate cramping, mild cramping.

Since it was actually something that was assessed by the independent observer and not the patient, we were wondering if that was actually a valid difference between mild, and moderate and severe?

So, one of the things we looked at was the overall cramping rate. And in my presentation I had said how in 94 percent of the UBT patients experienced any cramping at all, so, whether it be mild, moderate or severe, whereas 84.1

percent of those patients who had rollerball experienced some type of cramping.

And actually when you look at that statistically, the 94 and the 84.1 is not statistically different. So, the question is actually, although there is a difference between UBT and rollerball in the severe cramping, when you are looking at overall cramping, given the fact that it is not actually a validated measure, perhaps, we are sort of splitting hairs and maybe overall cramping is actually very similar between the two groups.

But that was the discussions we had as a review team.

DR. EGLINTON: Still adding? Dr. McColl? Dr. Loffer?

DR. LOFFER: Dr. Loffer. I thought possibly I could help further confuse this issue. There is a study being done in Holland which is done using our exact protocol. The difference is that the patients have been suppressed beforehand with a GnRH analog and they all received general anesthesia. In the rollerball 6 series--this is 25 in the rollerball, 29 thus far in the ThermaChoice--60 percent of the rollerball patients had no problem with cramping; 66 percent of the ThermaChoice had no cramping. Strong pain medications were required in 28

percent of the rollerball and only 13 percent of the ThermaChoice.

I, too, think our statistics are biased by our lack of control of the type of anesthesia and post-operative analgesics. I offered it as a confusing factor. These were all under general anesthesia. These were single anesthesia. Other than that, the only substantive factor was that they were all suppressed. That might be a factor, too.

DR. EGLINTON: I think, unless there's objection here on the panel, I think we're ready to move to question 3, which is, "Based on efficacy and adverse events data, do you believe that UBT is safe and effective as a treatment for menorrhagia in women?"

Does anyone want to live with this artificial split that the FDA gave us, greater than age 40, under age 40? Does anyone feel compelled to answer the question for under and over age 40?

DR. CHATMAN: I thought we answered that by saying premenopausal.

DR. EGLINTON: Premenopausal. Good enough for everybody? Okay, premenopausal.

So Dr. Harvey, do you want to show us what our choices are when we're voting? I think we're at the point of a discussion prevote here. What are the possible

outcomes of a panel deliberation? That's the slide we're looking for.

DR. BLANCO: We are going to discuss the other questions, right, and issues of labeling?

DR. EGLINTON: If we decide that we recommend that it's our opinion that it's safe and effective, then we need to talk a lot about labeling.

DR. PERLMUTTER: When we get to labeling we may want to approve this but with conditions on the labeling.

DR. EGLINTON: Exactly.

DR. PERLMUTTER: So I think we can answer 3 without necessarily going to the official vote.

DR. EGLINTON: If the answer is "no," we don't have to go on to page 2.

DR. PERLMUTTER: That's right.

DR. EGLINTON: This is time management 201. No squirming in the front row. That was just a joke. We lost the slide.

Dr. Perlmutter?

DR. PERLMUTTER: Can I make a motion?

DR. EGLINTON: Dr. Perlmutter, please.

DR. PERLMUTTER: I'd like to make a motion that on the basis of the data presented on efficacy and adverse events that the UBT is safe and effective for the treatment

of menorrhagia in the premenopausal woman.

DR. EGLINTON: Second?

DR. PERLMUTTER: Colin is moving towards the podium.

DR. EGLINTON: You can hold that thought because Colin is--

MR. POLLARD: I think I would like to go back to Dr. Eglinton's point that the form of the panel motion has to be either approvable, approvable with conditions or not approvable. I think it's not unreasonable for you to just take a general poll related to question number 3 and move on but I don't think you want a motion to vote until you've dealt with any possible conditions because part of that motion, if you are going to do approval with conditions, then you need to spell them out, as part of the motion.

DR. EGLINTON: So we have a motion on the floor that didn't quite get seconded.

DR. BLANCO: Maybe we should change it that rather than a motion, I have a fuzzy feeling that the efficacy and adverse events profile is tending to make me vote that we should approve this but I'd like to discuss other issues that may place some conditions on the approval.

DR. EGLINTON: As a matter of parliamentary procedure, would Dr. Perlmutter care to withdraw her motion?

DR. PERLMUTTER: I'll withdraw my motion.

DR. EGLINTON: Thank you.

DR. PERLMUTTER: And I'll become fuzzy, along with Dr. Blanco.

DR. DOWNS: Why don't you just ask informally how many people would vote no on that question?

DR. EGLINTON: I like that idea. Does anybody believe that they really, at this point, want to vote for disapproval when the time comes?

Does everybody want to go on and start talking about conditions, because that's probably what we're going to wind up voting for, as the time comes.

So that means everybody wants to go on to number 4, labeling. We said yes, we want to limit it to premenopausal women. Everybody happy with that?

Number 5, "Based upon clinical data presented by the sponsor, should a recommendation be made in the labeling for lower and upper limits of uterine size?" It seemed to me the sense of the panel was between 7 and 10 centimeters. Anybody care to discuss that or have a different impression of what the panel discussion was?

DR. CHATMAN: Is that a uterus that sounds to--

DR. EGLINTON: Sounds to 7, between 7 and 10 centimeters, 7 or greater or up to 10 centimeters, less than

or equal to 10.

Dr. Shirk, does that trouble you?

DR. SHIRK: No, I think that's reasonable. It answers the question of the small uteri and I think that's appropriate.

DR. EGLINTON: Dr. McColl?

DR. McCOLL: Dr. McColl, Gynecare. I'm just, in listening to the panel discussions, I guess I'm just trying to get an understanding here of why we would want to potentially label this product with the number 7 when we've seen significant numbers of cases already in the study that the device appears to be safe in that group at this point. We do have efficacy data in that group of patients. We've already discussed earlier about potential safety issues regarding the device itself and the shape and size of the device, and why we would need to label that at a 7 number more than in the 6 or 5 range?

DR. EGLINTON: I can answer that. Because the efficacy under 8 centimeters is 94.1 percent. The efficacy under 7 centimeters is around 50. That's significantly different.

MS. DOMECUS: But it tracked the same as the rollerball and I don't believe any rollerball labeling has--

DR. EGLINTON: We're not here to discuss whether

rollerball is safe and effective under 7 centimeters. We're here to discuss whether this technique is safe and effective under 7 centimeters and it's not effective, by their data. It may be safe but it's not effective.

MS. DOMECUS: But the rollerball was the control device that they're comparing it to to demonstrate safety and effectiveness.

DR. EGLINTON: But we're not here to approve rollerball under 7 centimeters. We're here to approve this technique under 7 centimeters. I understand and agree with you but we're not here to approve that or recommend approval for that.

MS. DOMECUS: I know. I'm just saying that that's what the gold standard is for the labeling for the rollerball and if this is being shown as trying to be safe and effective in comparison to the gold standard, why would it have stricter labeling?

DR. EGLINTON: Dr. Chatman?

DR. CHATMAN: Inasmuch as the data is so inadequate for these small numbers, maybe one of the conditions should be until we get more data on uteri of less than 7 centimeters.

DR. EGLINTON: Dr. Yin?

DR. YIN: I would disagree with Cindy because

we're not here to do a 510(k), substantial equivalence. We happened to use this product as the control. Each PMA, they have to demonstrate that the device itself is good for whatever purpose, whatever data that they have. We're not going to label this 7 to 10 centimeters in the indications for use, but it should be somewhere in the labeling because if it's something that we really do not want, we would have put it in the indications for use. I don't think that's what the panel is recommending. The panel is recommending that somewhere there should be advice to the physicians.

DR. EGLINTON: Dr. McColl?

DR. McCOLL: Certainly in the fact that the data is somewhat limited here, certainly from the company's side I don't think it would be appropriate from our position to put something in the labeling, possibly in the precautions or something, saying that there's limited data in this group of patients at this time.

DR. EGLINTON: Well, what we're troubled with is the data that exists do not suggest efficacy under 7 centimeters. It's a coin toss under 7 centimeters. It's 50 percent.

Dr. Loffer?

DR. LOFFER: Dr. Loffer. As a potential user of this device I would be very discouraged if I were forced on

uteruses that measured less than 7 centimeters to have to use the rollerball to perform an endometrial ablation. I grant you I can't argue with the low numbers and the apparent low success rate and I realize we're not here to validate the resectiscope but to limit us in that group of patients is going to require us to use a different method, which would appear, at least in our limited numbers, to be equal.

DR. EGLINTON: Well, we're not communicating. Number one, the data we have don't suggest it's equal. Number two, all we're talking about is how the product is labeled. The company could not advertise the product for use in a uterus under 7 centimeters. You, the practitioner, could use it in a uterus that measures 2 centimeters if that's your professional judgment of what you want to do.

Dr. McColl?

DR. McCOLL: We've had a chance to try to get the numbers to you that you were asking for and this may help possibly. Here again I think we're getting to sort of data-slicing again and it's hard to make statistical significance out of the data as we start cutting it in this order, but if we look at the results in the 6.5 range, most of the patients under 7, we had, for instance, four of the patients were between 6 and 6.5 and three of those four were

successful.

So I guess my point is we're going to get smaller and smaller numbers but clearly there were patients, three out of four, in the 6.5 range that were successful.

DR. BLANCO: My concern, I don't want to be into data-slicing and that's why we didn't do it for the 40 age group. But whether you say it's equivalent or not equivalent, it just looks to me, like in the small number you've got, that there's something different in the small uterus, okay, than in the bigger uterus.

Number one, if you have so few numbers, I'm not sure that this makes such a big impact in how many women you're not going to be able to use it in.

The other issue is if you've got foreign data or other data and you look at the subset, that's new data to bring in what the success rate is for that. But I think with the small number, and not trying to slice the data, this is a new procedure that's going to be let out on the market and it's not like the success rates were the same in the 6 to 7 centimeter as everywhere else and you just had 15 patients but you would expect that everything else would be the same. I mean, you've got a much higher failure rate from both procedures.

You have a 40 percent failure rate versus the much

lower failure rate in the over 7 centimeters in the data that you've presented. So is there something different about this uteri? To me, that's what comes to mind. Is there something different about these uteri that maybe neither rollerball nor this procedure is quite the best indication for these patients? I mean, why is the rate different? That's the concern that I have, not trying to slice the data to the smallest numbers, but there are other differences besides just that you've got small numbers. I mean, there's a difference between this and the rest of the population.

DR. MAPLES: I want a clarification. Are we asking the manufacturer to change the labeling to make it mandatory only to use this product in the 7 to 10 centimeter range, or are we asking just for a statement saying the data is insufficient for use in uteri that are less than 7 centimeters? To me it's a lot different, actually saying we only can use this between 7 and 10 versus the data's not there.

DR. BLANCO: Well, how would you like to see it?

DR. MAPLES: I would prefer to say the data is not available at this time, rather than limiting it completely.

DR. EGLINTON: Dr. Downs?

DR. DOWNS: At the risk of making things worse,

I'm troubled by some of these numbers. Less than 7? There are eight successes out of 17. That means there are nine failures, right?

DR. BLANCO: No, seven failures. Total of 15 and seven failures, eight successes.

DR. DOWNS: Okay, seven failures. And then less than 8, for 95 percent success rate, you've got to counteract those seven failures, which means you have to have well over 100 women less than 8 centimeters, and I thought it was only a fourth of them or something like that.

DR. EGLINTON: It's supposed to be 94.1 percent effectiveness under 8 centimeters.

DR. DOWNS: Maybe what you did during the noon hour is wrong.

DR. EGLINTON: What are we talking about? Fifty patients under 8 centimeters, 25 in each group roughly, ballpark. And of those, we have seven and a half under 7 centimeters.

Dr. Yin?

DR. YIN: As long as we have very small numbers, I think what the company is recommending is that if they put it under precautions, that does not say contraindication. So I think that's what Dr. Maples--that's what you're looking for. The minute they put it in precaution, that is

not "cannot." It's just lack of data or something like that, okay?

Now, if they cannot do it you're going to put it under contraindications, if there's some safety problem.

DR. EGLINTON: I don't think anybody was really talking about contraindications. It's just indications. It's indicated for use in a uterus that sounds from 7 to 10 centimeters. That's all. I think that's the sense of what people were saying.

DR. YIN: But if you do the indication, that's very limited, too. But if you leave it as a precaution, then the physician can try, if it's good enough for the purpose they need. But if you put it in the indications, that ties the company's hands.

DR. BLANCO: So you're saying to say something like the indication is 6 to 10, but in the precautions it would say uteruses below 7 centimeters--the data for uteruses that sound below 7 centimeters is limited as to its success rate? Is that what you're saying?

DR. YIN: You would not put that in the indication because once you put it under the indication, you limit this product. We leave it much broader this way if it's under the precautions.

DR. EGLINTON: That's probably making us more

confused, Dr. Yin, because there has to be a lower limit somewhere. It's not 0 to 10 centimeters. Nobody likes 4 to 10 centimeters.

DR. YIN: That's why your precaution can make it very strong for the precaution.

DR. BLANCO: Before we go on, I think Dr. Downs brings up a good question. Maybe we're talking about data that you all put together over lunch and maybe it's not correct. If you had seven failures, if I saw your other slide, you had something like a 90 something percent success rate in the less than 8 centimeter group, so you have to account for those seven failures in that group and your numbers--it doesn't seem to be adding up. I mean, you'd have to have a huge number in the less than 8 centimeters. Do you understand what Dr. Downs was saying and what I'm bringing up? Let's make sure we're talking about appropriate data.

DR. EGLINTON: Dr. McColl?

DR. McCOLL: Dr. McColl. I guess my only comment is we certainly can relook at our data as we're trying to calculate it on a very quick basis here and possibly, at the break, come back to you with more information if that's helpful.

DR. SHIRK: I think the issue right now is

basically we have limited data. Is it inappropriate to simply ask the company to basically supply more data to get rid of the labeling issue? I mean I think it's a totally confused issue right now. It's like they don't have any data. The numbers would not be huge to get significant data to correct the issue, so I guess my feeling would be that it's still appropriate to leave the labeling from 10 to 7 centimeters until we get data, until the company can supply data to remove that.

DR. EGLINTON: That's really the focus of the discussion, is we believe, or at least it sounds to me like we believe there are sufficient data for women who have a uterus that sounds from 7 to 10 centimeters to believe this is a safe and effective technique. For women who have a uterus that sounds under 7 centimeters, we haven't been presented with data.

So at this point it's kind of looking like not approvable or approvable from 7 to 10 centimeters. That's the way the discussion seems to be drifting. And if it's approvable from 7 to 10 and the company happens to gather up some more data next year under 7 centimeters and wants to come back and ask for a change in the labeling because it's 97 percent effective, that's great, but we don't have those data today.

Dr. Perlmutter?

DR. PERLMUTTER: Can we do this as Dr. Yin has suggested and put this in as a precaution because we only have the data on the 7 to 10 centimeters and then ask for post-marketing surveillance and do the follow-up on the 4 to 7 centimeters that way?

DR. EGLINTON: Using that line, then, what's your lower limit? Uterus not over 10 centimeters, and no lower limit?

DR. PERLMUTTER: Well, the only data that's been presented to us is 4 centimeters, which sounds awfully small to me but that's the data they have and they have data on it. So we could, in the precautions section, put this statement in there.

DR. EGLINTON: The question would be what is the smallest uterus that they did? Did you do a 4?

DR. PERLMUTTER: Four centimeters.

DR. EGLINTON: Did you do one of them at 4 centimeters?

DR. PERLMUTTER: Two or three, wasn't it?

DR. EGLINTON: Three of them at 4 centimeters?

DR. PERLMUTTER: Those numbers are really--they're not statistical. Nobody's going to argue with that. But can we do it with a post-marketing surveillance follow-up

rather than tying their hands, which isn't fair because there's no data either way?

DR. EGLINTON: We have an obligation to make a decision based on data and you just said it--there are no data. We have to make a decision based on data.

DR. PERLMUTTER: But it's not harmful.

DR. EGLINTON: Go ahead.

DR. MAPLES: The data that we showed, the numbers are small. There were no complications in the group. So I think again, a precautionary statement that there's insufficient data but I don't see a safety issue with the small uteri.

DR. CHATMAN: We're talking about efficacy and safety, though.

DR. EGLINTON: The only thing that we have seen is that under 7 centimeters, the efficacy is a coin toss. So is that efficacious?

DR. PERLMUTTER: But I'd have to argue with that, Gary, because in their initial slide it showed a 94.1 percent success rate in the less than 8 centimeters and that stuck in my head because my response to that is maybe they didn't need it to begin with and that's why you got such a high response rate. But they had good data, so I don't know how they came out with the 50 percent.

DR. EGLINTON: We're trying to reconcile that. There aren't any more than about 25 patients in each group under 8 centimeters and if we've got seven failures, three and a half in each, how did we get up to 94 percent success? Something doesn't sound like it adds up.

DR. BLANCO: Could we bypass this one and have them take a look to make sure they've got their data correct for that lower number and maybe we can come back to this one?

DR. EGLINTON: That's what I'd suggest, going on--some furious whispering and paper-shuffling in the first two rows here while we go on to question 6.

"Is the proposed contraindications section appropriate?"

DR. PERLMUTTER: I have a question about the patient with any anatomic or pathologic condition in which severe thinning or weakness of the myometrium could exist. I guess what I need to know is in some of the information in this material that we got, they talked about myomectomies where the lining of the uterus had been--where the uterine cavity had been entered and classical Caesarian section was mentioned a couple of times. Should that be spelled out?

The other thing that I'd like to know is was this procedure done on anybody with a lower segment Caesarian

section? I'd like to know what data we have on that because you're saying it's safe.

DR. EGLINTON: At the time of repeat Caesarian, we often see what is described as a uterine window, which basically is there's almost no uterine myometrium. There's no myometrium between the endometrial cavity and the serosa. Are those patients--and there are a lot of those patients--are those patients okay for this procedure? And how do we know that?

DR. GRAINGER: In the study, the clinical trial, in the UBT arm, there were 19 patients that had had one C-section, 17 patients that had had two, two that had had three and one that had had four. You can see the numbers for the rollerball--ten, seven, six and one.

So almost a third of the patients in uterine balloon therapy had had at least one low transverse Caesarian section.

DR. PERLMUTTER: Okay.

DR. EGLINTON: Do we know anything about complications in that group specifically? Any kind of problems?

DR. GRAINGER: There were no complications in this group.

DR. BLANCO: I think that answers the question.

You know, these were all low cervical transverse?

DR. GRAINGER: Yes.

DR. BLANCO: I would agree with you that for classicals--certainly for prior classical, that should be spelled out not just something that thins it out because we all know that does thin it out. So it should be put in there that that's going to be an issue.

I don't know about myomectomy. I guess I'd like to maybe hear some more discussion about that.

DR. PERLMUTTER: I thought I had read that in some of the material that they had submitted to us, that previous myomectomy where the cavity had been entered was considered a contraindication. Did I misread that?

DR. BLANCO: Then it should be spelled out.

DR. PERLMUTTER: Dr. McColl, did I misread that? It's in there, isn't it?

DR. McCOLL: Maybe you could re-ask the question so I can understand.

DR. PERLMUTTER: In either some of your prior labeling brochures or in some of the material that you handed to us it was spelled out that both classical Caesarian section and myomectomy where the cavity had been entered should be considered contraindication to this procedure.

DR. McCOLL: I'm not sure it was listed as contraindication because that's the labeling that we've submitted in that direction.

DR. MAPLES: It was exclusion criteria.

DR. PERLMUTTER: It was exclusion criteria.

DR. MAPLES: It was there someplace.

DR. BLANCO: I read it, too.

DR. SHIRK: One of my questions would be basically if they did an SIS ultrasound, which is part of the work-up or could be part of the work-up, would this not rule out the problem?

DR. PERLMUTTER: Well again, we go back to if they've not done it and this was exclusion criteria then we have no information to state whether or not you have a problem.

DR. SHIRK: But the indication for--one of the work-up criteria for these patients would be that they either have a hysteroscopy and/or a saline infusion sonography, so that in either one of those instances, any kind of defect--I mean, as far as a good preoperative work-up, if we enforce a good pre-operative work-up that should help at least screen out those patients with those kinds of problems, unless you're worried about the balloon rupturing the uterus.

DR. PERLMUTTER: I'm not worried about the balloon rupturing the uterus. I'm more concerned about heat transfer. But I don't remember seeing hysteroscopy as part of the--it was part of the protocol but I don't remember seeing that as part of the labeling for what physicians should do as preoperative work-up.

DR. SHIRK: The question would be are we going to have in the labeling process, you know, the same kind of criteria they had in their study as far as work-up?

DR. PERLMUTTER: We haven't gotten there yet.

DR. SHIRK: I understand.

DR. EGLINTON: We're not really talking about work-up. If a protocol is conducted and an exclusion criterion is listed as a description of the protocol, then clearly that exclusion must also be listed in the labeling because those patients were not studied. So we clearly have no data on those patients, so we can't entertain approving a product for use for that indication. It hasn't been studied. It's not part of the PMA.

But can anyone come up with those two exclusion criteria, the classical Caesarian and the cavity entered with previous myomectomy? Several people remember it but they can't find it.

Dr. McColl?

DR. McCOLL: I'm just trying to get clarification here. This is what we're talking about, the contraindications, second to the last bullet point; is that correct?

DR. PERLMUTTER: Yes.

DR. EGLINTON: Dr. Harvey?

DR. BRIAN HARVEY: Brian Harvey. Just as a point of clarification, in the original summary of safety and effectiveness of the PMA on page 8 in the bold numbering, under potential adverse events of the device, on perforation of the uterus--correction--actually rupture of the uterus, they're saying, about four lines in, "Use of the balloon therapy in patients with previous uterine surgeries, which might thin the uterine musculature, such as full thickness myomectomy or classical Caesarian section, is contraindicated."

So actually it is in that section but in the actual device labeling, under the contraindication section, that's not listed. So there is a discrepancy between the summary of safety and effectiveness and the device labeling.

DR. EGLINTON: Dr. Perlmutter, what you're lobbying for is for that statement that Dr. Harvey just read to be included in the contraindications?

DR. PERLMUTTER: That's correct.

DR. EGLINTON: Is there any other discussion on that particular point?

DR. BLANCO: Could you repeat reading it again?

DR. PERLMUTTER: It says that "Use of balloon therapy in patients with previous uterine surgeries which might thin the uterine musculature, such as full thickness myomectomy or classical Caesarian section, is contraindicated."

DR. EGLINTON: Any other discussion on that point?

DR. BLANCO: The only other issue is the only way you could do it is to put in here, and this is just an issue Dr. Shirk brought up, I don't think a lot of people are necessarily going to do a hysteroscopy or hysterosalpingograms or other things to find the thickness but if you put it the way it's worded there and add the specifics of classical Caesarian section and myomectomy, it does allow the option that if somebody did want to go with a procedure to look at the thickness of the myometrium, then they could use it.

It's a minor point and few patients and we may not even have data to really answer whether it would be safe, but I just throw that out. I think I'd go with just putting the statement as it was put in the original study.

DR. PERLMUTTER: I'm concerned because of heat

transfer. And although we know about no minimal heat transfer with full thickness, we don't know about it in a thinned uterine wall. My concern is safety.

DR. BLANCO: And if you blow it up to get the pressure up, you may actually distend the uterus enough where you'd thin out that area.

DR. EGLINTON: Even more so, right.

Could I ask--I'm sorry; Dr. Shirk?

DR. SHIRK: I have another thing I want to bring up about the contraindications.

DR. EGLINTON: Go ahead.

DR. SHIRK: It says cervical cancer or atypical endometrial hyperplasia. I think it's pretty standard that any endometrial hyperplasia is off-limits as far as endometrial ablation, not just atypical endometrial hyperplasia. I think that needs to be amended to endometrial hyperplasia, not atypical endometrial hyperplasia.

DR. BLANCO: If it's cystic hyperplasia, you feel that way?

DR. SHIRK: Rich Gimpleson did a whole study, got all together the patients that have developed endometrial cancer across the country and almost to the patient, all of them have had endometrial hyperplasia. One of them had

simple hyperplasia as a diagnosis, preoperative diagnosis. But certainly adenomatous hyperplasia is a total contraindication.

Obviously we're trying to split hairs but--

DR. BLANCO: No, I agree with you. I think any kind of adenomatous hyperplasia, it shouldn't be used, but I don't know the progression from cystic hyperplasia to cancer, which is what you're concerned about.

DR. SHIRK: I understand what you're trying to say. Just for simplification, I would just say endometrial hyperplasia. I guess you could say adenomatous hyperplasia or atypical endometrial hyperplasia but certainly that also becomes a pathological criteria.

DR. EGLINTON: Could you be comfortable inserting the word "current"? Any devotee of Dr. Woodruff could certainly just blast the patient with enough progestational agent and convert that to some kind of nonhyperplasia.

DR. SHIRK: I think that's what we're pointing to, is that whatever--a lot of these patients have been treated that way and then came back and developed endometrial carcinoma. I mean, what is unique about the patient who develops endometrial hyperplasia in the first place, so that those patients certainly are, whether you treat them--if you treat them with progestins, then you'd better be able to

follow them for a long period of time on high-dose progestins or they're going to revert, a lot of them, anyhow.

DR. EGLINTON: Dr. Loffer?

DR. LOFFER: Four of those five patients were all post-menopausal, which we're not talking about, and I do certainly agree with you in that area. The other patient was a chronic anovulator at the age of 30 something when she had her procedure.

I think my concern, to include all hyperplasia, at least in Phoenix we have board pathologists that look at hundreds of samples of D&Cs and they finally find two glands that are slightly close together and they can call it hyperplasia. I don't think those are the patients we want to eliminate.

DR. EGLINTON: I don't know how to resolve that. I know exactly what you're talking about.

DR. SHIRK: If you have adenomatous hyperplasias as a diagnosis, would you advocate that these patients be treated we progestins and then procedure with an ablation? I don't think that's appropriate therapy and certainly the--

DR. LOFFER: I would assume those patients would be treated with hormonal medication and would respond to hormonal medication.

We're in total agreement with the post-menopausal patient, which is where most of this problem is going to be found.

DR. SHIRK: I still don't feel that I'm comfortable treating somebody that's got a diagnosis of adenomatous hyperplasia with endometrial ablation, nor is it appropriate.

DR. BLANCO: So you want to drop the atypical? How would you like it to read? Drop the atypical?

DR. SHIRK: I just suggest we leave it endometrial hyperplasia. The question there becomes a question of, as you pointed out, the cystic or the few glands of hyperplasia but it probably should read, then, adenomatous or atypical endometrial hyperplasia.

DR. MAPLES: I would prefer that to read adenomatous or atypical, rather than the broad hyperplasia because, as you said, you can get a couple of glands and call it hyperplasia.

DR. LOFFER: You will be eliminating the patient who may be a chronic anovulator, an infrequent ovulator who builds up--has an adenomatous hyperplasia who, when you cycle on progesterone, still floods. You will be eliminating that patient.

DR. BLANCO: I guess the issue there is what I

think Gary was trying to point out. That is if you've got someone who's got hyperplasia, you're going to medically treat that patient and you're going to check to see whether they've responded to that. If they respond to the medical therapy then you're not going to really do any of these procedures. If they don't respond, if they still have an adenomatous hyperplasia, then what Dr. Shirk is saying is the best treatment is not this procedure.

The issue then is if they don't have it anymore, if the medical therapy cured their adenomatous hyperplasia but they still have menorrhagia, would they then be candidates? I mean, we're really picking fine hairs here. I think that's what you were trying to point out, Gary, in terms of once somebody's who's ever had the diagnosis once or is it somebody who has it currently?

DR. SHIRK: Again, the question comes down to underlying causes of endometrial hyperplasia and the question of if you treat a patient with the progestational agents, obviously a significant number of them are going to resolve the endometrial hyperplasia.

The question is once you stop the progestin therapy, how many of those patients revert and go back to having endometrial hyperplasia? It's sort of a life-long thing of monitoring these patients. I don't disagree with

treating them conservatively with progestins but the question is basically if you have a patient that has endometrial hyperplasia and you go through the course and it goes away and then you stop the progestational therapy because the patient doesn't like the progestins, I mean, a lot of women do not like progestin therapy. Then a patient reverts back to having significant menorrhagia and then you do an ablation. Have you really changed, you know, her risk factors over time? I don't know.

DR. EGLINTON: I think what you're suggesting is based on the anecdotal survey that is available in the literature thus far, women with any degree of endometrial hyperplasia represent a very high-risk group for endometrial ablation. That's what we know so far.

DR. SHIRK: Right.

DR. EGLINTON: And with this particular technique, since it requires more than six or 12 or even 36 months of follow-up, we can't know anything about the safety in that group with this technique.

So the safest thing to do is to eliminate those patients from consideration for this technique until further data is available? Is that fair?

DR. SHIRK: That's fair.

DR. MAPLES: That's fair.

DR. EGLINTON: Dr. McColl?

DR. STABINSKY: I'm Dr. Seth Stabinsky. I'm a clinical assistant professor of gynecology and obstetrics at Stanford and I work full-time for Gynecare. I'm the associate medical director.

I'm a little bit confused about the question of adenomatous hyperplasia here because my understanding is that the concern that we have about the progression to endometrial cancer is in patients with atypical adenomatous hyperplasia. Otherwise we'd be advocating doing hysterectomies on a large number of patients with simple adenomatous hyperplasia and not hyperplasia with atypia.

So I'm just not exactly sure how--we should be doing hysterectomies on very large numbers of patients with adenomatous hyperplasia if we're fearful that that's going to go on and turn to cancer.

It sounds to me that the issue or the concern really is what should our follow-up be on high-risk patients who are treated with any form of endometrial ablation, whether that be by rollerball or by the balloon technique, and I'm not sure that we really know what the follow-up should be on these patients. Should we be doing ultrasound? Our concerns are are they going to go on and bleed and will we recognize that later?

But high-risk patients, patients who are at high risk for atypical hyperplasia or cancer down the road, we need to have a method of following them down the road.

DR. BLANCO: I don't think that that's quite the way to frame the question. I don't think the issue is one that we're missing out on a lot of people that should go to hysterectomy. I think the issue is we have a new procedure, a new way of managing a problem and we have to be concerned in that we don't know what this type of ablation is going to do to someone that has adenomatous hyperplasia and may have a progression into other problems.

That doesn't mean you're going to do a hysterectomy on every single one. It means that until you see some data of what happens to the endometrium of patients with adenomatous hyperplasia under some research protocol with heat ablation, it may not be the safest thing to do.

So I don't think you frame it in an issue of hysterectomy.

DR. EGLINTON: Dr. Perlmutter?

DR. PERLMUTTER: I've got a peripheral question that may answer this one. You've done hysterectomies on some of the women who have had the balloon therapy. Can you tell me what the uterine cavity looked like, whether there was any endometrium left, whether this was all synechiae.

What information can you tell me because that may help us resolve this issue.

DR. EGLINTON: And also, since you had a tissue diagnosis, you had histology on all of these patients, both arms of the study pre-op, how many patients in the study had what degrees of endometrial hyperplasia?

DR. McCOLL: Dr. McColl. We're looking at data right now and we should have that to you relatively quickly here.

DR. EGLINTON: The problem here is really one of follow-up. To rephrase or paraphrase what Dr. Shirk has said, if we're afraid that these women who have endometrial hyperplasia have an underlying pathology, an etiology for that and they get ablation and they disappear from follow-up because they're not bleeding disastrously anymore, we may very well alter the natural course toward neoplasia for those patients.

We may alter it or we may fail to pick it up when it's early in the course as characteristically, a woman who is not ablated, she doesn't get away from us because she bleeds all the time and we pick her up early. If this woman isn't bleeding all the time then we'll lose her.

Can I ask another question on the contraindications? A patient with active genital infection

at the time of procedure. Can we make that more specific? Does that mean vaginosis? Does that mean clinically insignificant yeast in the vagina? Does that mean herpes all over the vulva? I mean, what does that really mean, active genital infection? What do you envision? Who's contraindicated?

DR. LOFFER: I think primarily those patients that might have a gonorrhea or chlamydia.

DR. EGLINTON: Is it a requirement in the labeling, then, that a patient have some sort of DNA probe testing before the procedure?

DR. LOFFER: Loffer. That's certainly not standard practice for endometrial ablation as it's currently practiced. I think it's just the obligation of the physician to assess the patient and to, if they reason to be concerned, to rule out or verify that she doesn't have an active infection.

DR. EGLINTON: But the people who now do rollerball therapy are exceedingly well trained, experienced, highly skilled clinicians who investigate their patients like crazy before they do this procedure. And now we're talking about a balloon that every yo-yo in the country can stick in the uterus in the office without any pre-op evaluation. That's really what we're talking about.

So we need to--I'm not arguing, but to protect the patients, we need to spell some things out. We're talking about protecting real women here. These are real women's lives. Somebody needs to tell all these people how to protect these women from being harmed.

DR. LOFFER: What I didn't indicate in my answer, which I thought was self-evident, was pelvic inflammatory disease. That also would be included.

I would personally see no problem with specifying gonorrhea, chlamydia or active pelvic inflammatory disease, for the yo-yos.

DR. BLANCO: Licensed yo-yos.

DR. EGLINTON: Most of them are licensed, yes.

DR. LOFFER: My main current interest is the yo-yo.

DR. BLANCO: For protection, it would seem to me that the more general statement is much more protective. If you want to be specific, I think you could say an active genital infection at the time of the procedure, such as salpingitis, pelvic inflammatory disease, chlamydia, gonorrhea and if there are others that we can think of. But I guess I wouldn't want to just say salginitis, something like that, and then have a big old herpetic lesion or something right at the cervix and use this procedure,

although it may be perfectly safe--I don't know.

But I like the general statement and then if anything, just add a couple of specifics where it makes clear sense that we shouldn't be doing it.

DR. EGLINTON: That's what I'm asking for, is some specifics to be added. The people who are doing this right now obviously know what to do and what not to do but not everybody in the future is going to know that.

DR. PERLMUTTER: Gary, what if you modified it to say active upper tract genital infection? Then your vaginitis and your vaginosis would be excluded.

DR. EGLINTON: Does that make sense to everyone? Cervicitis?

DR. BLANCO: I would say you've got to include the cervix, too.

DR. MAPLES: I think you have to say cervicitis.

DR. EGLINTON: How about--we haven't heard any discussion about herpetic lesions, active herpetic lesions. Does anybody have any feel for that? Any of the investigators have any feel for that?

DR. MAPLES: They were excluded.

DR. EGLINTON: Is that one of the exclusions, active herpetic lesion?

DR. BLANCO: Yes.

DR. PERLMUTTER: Gary, Lillian is willing to go and get the IUD wording on this to see how that is worded because this is not that dissimilar from that.

DR. EGLINTON: Exactly.

DR. YIN: It's exactly the same thing.

DR. EGLINTON: Sure.

Yes, sir?

DR. GRAINGER: Dave Grainger. You'd asked some questions about the hysterectomy specimens. The four patients that underwent hysterectomy that were treated by UBT, in one, the endometrium was barely visible, being less than 1 millimeter in thickness and described as weakly proliferative. In the second one the endometrium was not described but there were fibroids present. In the third, the endometrium was .2 millimeters in thickness and in the last patient the endometrium was .1 millimeter.

DR. PERLMUTTER: What period of time following ablation therapy did these hysterectomies occur? Do you know?

DR. GRAINGER: The first patient that I described had completed a year.

DR. PERLMUTTER: That was the .1?

DR. GRAINGER: Yes. I'm sorry, 1 millimeter. These were millimeters--I'm sorry.

The second patient had a hysterectomy after her six-month follow-up.

DR. PERLMUTTER: That's the one with no lining noted but she had fibroids?

DR. GRAINGER: Fibroids. And actually the uterine volume at the time of that--at the time of the UBT, the uterine volume was greater than 30 cc's but the procedure was done we just 30 cc's in the balloon.

And the third patient had UBT on 5/11/96 and had a hysterectomy one year later, 5/2/97. That was 2 millimeters of endometrium. The fourth patient was treated on 5/29/96, had a hysterectomy in November. So from May to November. That was 1 millimeter in thickness.

DR. PERLMUTTER: Were there intrauterine adhesions with the synechiae? Is this like an Asherman syndrome? Because there was one of the reports in here that discussed adhesions anteriorally and posteriorally and never said where those adhesions were so I didn't know. I assume they were intrauterine but it didn't say that.

DR. LOFFER: The more the surfaces are disrupted, by whichever technique, the more chances of scarring. There appears to be less scarring with the thermo balloon because it doesn't really disrupt the surface. It doesn't create open areas.

DR. PERLMUTTER: So if we needed to do a D&C afterwards it's not going to be that difficult to do?

DR. LOFFER: To answer your question in a slightly different way, you probably would evaluate the patient by ultrasound. You should be able to do an endometrial biopsy and hopefully a D&C. I don't think anybody could promise you that but these cavities tend to stay open--I mean the UBTs.

DR. GRAINGER: Just to follow up on what you were talking about, the adhesions anteriorally and posteriorally, those were pelvic adhesions and not intracaviteric adhesions.

DR. PERLMUTTER: Thank you.

DR. EGLINTON: Any other discussion of contraindications?

DR. SHIRK: What about sterilization or contraception? I guess that's another issue.

DR. PERLMUTTER: That's not a contraindication.

DR. EGLINTON: That is question 7, immediately after. We could certainly include that.

Any other discussion of contraindications anybody wants to bring up?

Okay, question 7, Dr. Shirk.

DR. SHIRK: I think basically the question here is

basically the risk of pregnancy or the means of contraception after an endometrial ablation procedure. Certainly this is not a sterilization procedure. Several patients have gotten pregnant after endometrial ablation. It creates significant problems or can create significant problems with these pregnancies.

So the issue comes down to if a large number of patients have the procedure and opt not to get sterilized, at what risk are these patients of having abnormal pregnancies that would include increased risk of miscarriage, increased risk of problems with utero-placental profusion and/or increased risk of placenta accreta at the time of delivery?

Probably we've demonstrated that all of these above are possibilities in these patients and I guess the question is how do we deal with this issue regarding contraception or contraceptive warnings in a patient that's had the procedure?

DR. EGLINTON: Dr. Perlmutter?

DR. PERLMUTTER: I would assume that would go into a warning section. Patients should continue contraception or be sterilized.

DR. EGLINTON: Is that sufficient? Dr. Chatman?

DR. CHATMAN: I don't think it's sufficient. I

think that intrauterine growth retardation and all kinds of other pregnancy-related problems can be foreseen reasonably to come from the lack of contraception used with patients who have this technique done. So I think it should be something much stronger than that. I'm not sure what, though. We can't insist that people get sterilized.

DR. SHIRK: Certainly it should be a recommendation that sterilization--that if a patient's not been sterilized that they strongly consider it with the procedure.

I mean, the real issue here is that the procedure, whether we like it or not, is going to become essentially a cosmetic type of procedure. We're obviously talking about issues but in the reality of this world, none of us are naive enough to think that this procedure is not going to be used significantly for nonpathological situations and I think it's going to essentially expose a large population of women to some potential reproductive problems that so far they've not been exposed to and certainly could be a significant medical-legal issue down the line, not only for the companies.

So I think it's certainly a big issue that we don't need to just gloss over.

DR. EGLINTON: Dr. Maples?

DR. MAPLES: Can we be more specific in terms of the labeling, just saying you advise sterilization, but actually outline every one of these potential complications, so it's in the labeling? Would that help clarify for the physicians?

DR. SHIRK: I think certainly a warning that severe pregnancy complications may occur--

DR. MAPLES: Such as.

DR. SHIRK: Yes.

DR. EGLINTON: Dr. McColl.

DR. McCOLL: McColl. Currently in the labeling that we've submitted, this is not under a warning section but we have listed significant issues with pregnancy and pregnancy following endometrial ablation, et cetera, so that part has been put into the labeling in the present form right now. It's not in the warning section but it is in the labeling at this time.

DR. ELISA HARVEY: The panel members should all have a copy of the labeling in their folders that they can refer to.

DR. McCOLL: I think it's at page 12. It says "Pregnancy following endometrial ablation is rare but can be dangerous. The risk of placental implantation abnormalities, spontaneous abortion and/or fetal

malformations may be increased after ablation. Patients who carry to term may be at higher risk of placental accreta. Patients who become pregnant after any ablation procedure should be appropriately and thoroughly counseled. For non-sterile patients contraceptive should be continued following any endometrial ablation, including uterine balloon therapy, even if menstrual flow is eliminated completely."

DR. MAPLES: I think that's very specific.

DR. McCOLL: In bold print, "UBT cannot be considered a sterilization technique."

DR. EGLINTON: Dr. McColl is reading from the thermal balloon ablation system manual for the provider, which is good. I think--

DR. MAPLES: I think that's very good.

DR. EGLINTON: It would be good to include that same wording in the patient brochure, I think is what panel members are talking about.

DR. SHIRK: Right, I think the patient brochure needs to--the patient information on this procedure has to include significant warnings about pregnancy and the hazards about pregnancy.

DR. EGLINTON: So if that statement from the manual were included in the patient brochure, would that satisfy the panel members?

DR. MAPLES: I think it would be too medical. I think it has to be brought down to a proper language for patients to understand.

DR. BLANCO: Well, this is what it says for the patient in the brochure. "Can I get pregnant after treatment?" It's in a box. "This therapy should not be used if you ever want to have children. In fact, pregnancies after ablation can be dangerous for both fetus and mother. However, since there's a slight chance that pregnancy could occur, contraception or sterilization must be used after treatment."

DR. EGLINTON: Is that strong enough?

DR. SHIRK: I guess the question is with this, do we know what the risk of pregnancy is? Is it a slight chance of pregnancy? I think "slight" ought to be deleted.

DR. MAPLES: Since there is a chance.

DR. EGLINTON: Right, cross out "slight."

DR. McCOLL: McColl again. I guess the only comment is we haven't had any pregnancies from the IDE study to comment on. In fact, the international studies, the same thing. So I can't give you data to support, one way or the other, what that percentage is.

DR. EGLINTON: We have three in our department after rollerball.

DR. CHATMAN: The "slight" tends to minimize the risk and I think I agree with Dr. Shirk.

DR. BLANCO: Delete the "slight."

DR. EGLINTON: Does that satisfy people, delete the "slight"? Okay.

DR. PERLMUTTER: However, before you leave that page in the patient brochure, and that's page 2 on the patient brochure, in panel 3, the second picture, it says, "The fluid in the balloon is heated to 87 degrees and maintained for eight minutes while the uterine lining is treated."

I have a lot of difficulty with the 87 degrees. Our institution is still in Fahrenheit. When I first read this stuff it was sort of like 87 degrees, isn't that nice? It's not that hot. Then I'm going, well, how does that ablate the endometrial lining?

Again we're going to go back to the local yokel who's going to be using this device--

DR. BLANCO: The yo-yo.

DR. PERLMUTTER: I think that the 87 degree is misleading in the patient brochure and I think it's very misleading in the physician brochure and I'd like to see that either given both in Celsius and Fahrenheit or only in Fahrenheit. This country has not converted over to Celsius

yet.

DR. EGLINTON: I think everybody agrees with that.

DR. BLANCO: Yes.

We're down to question 9.

MS. YOUNG: We haven't finished with 8.

DR. EGLINTON: Oh, do we have more on the patient brochure? I'm sorry. I didn't mean to rush you. I'm sorry.

MS. YOUNG: Yes, I have a couple of things that I would like to bring up. First of all, I would like to say that I'm encouraged--I'd like to say this to the manufacturer, that I'm encouraged that we have a device that has the potential for reducing the rates of hysterectomies. I've been a patient advocate for over 25 years and have been concerned for a long time about excessive use and possibly unnecessary use of hysterectomy. So, as I say, I'm encouraged that we have a potential device here that could reduce those rates.

A couple of points that I'd like to bring up. First of all concerns the wording about latex sensitivity and allergy. This is a potentially very serious problem and there are two things here. I want to make sure that we all agree that all women in the education group to which this brochure has been addressed--what are we talking about?--six

or seven years of education, I think--know what latex is, that, in fact, it's a form of rubber and maybe the word "rubber" should precede "latex."

The other thing is that I think that there should be an emphasis, more of an emphasis about the danger of latex sensitivity, perhaps by putting it in a box, as has been done with some other concerns.

The FDA already has latex labeling required for medical devices, which has actually a cautionary statement on it, which is, "Caution: This product contains natural rubber latex, which may cause allergic reactions."

So, as I say, I feel that we should give more emphasis in the patient brochure on that particular area.

I notice that you've got a bit of white space on your patient brochure and so I'd like to suggest the addition of something which came to mind, which was the possibility of adding a section on, and I'm just putting this in quotes, "What potential complications should I watch for after the procedure?" And then perhaps make a statement like "Complications are rare but you should keep an eye open for" or however you want to word it, for something like fever, high temperature or purulent discharge or something like that. I just feel that that should be also included in the patient brochure.

CHAIRMAN EGLINTON: Can we hear again, this serous discharge, is that encompassed in the next 7 to 10 days? In the patient brochure on what we have labeled as page 2 on the far left, the bottom illustration, the text says, "Your uterine lining has been treated and will slough off like a period in the next 7 to 10 days." Does that describe the upper limit of the discharge that goes on after the procedure, or is it longer than that? Oh, okay, I see. In the middle column, it talks about a month. All right. That has that. Okay.

While people are looking at the patient brochure in terms of the wording on contraindications for a patient with active genital infection at the time of the procedure, we have from the '95--up to date, the FDA has the 1995 PDR.

DR. YIN: It has never changed.

[Laughter.]

CHAIRMAN EGLINTON: This means that classics never go out of style? Okay. For the Paraguard T380A intrauterine copper contraceptive, under contraindications, Item 7, the wording is "untreated acute cervicitis or vaginitis, including bacterial vaginosis, until infection is controlled."

DR. YIN: And that's a drug product. There's no IUD considered as a device anymore.

DR. BLANCO: Would you read that again?

CHAIRMAN EGLINTON: "Untreated acute cervicitis or vaginitis, including bacterial vaginosis, until infection is controlled."

DR. BLANCO: Nothing about endometritis?

CHAIRMAN EGLINTON: Yes, that's a contra-indication. Postpartum endometritis or infected abortion in the past 3 months, acute pelvic inflammatory disease or a history of pelvic inflammatory disease. Those are the-- conditions associated with increased susceptibility to infections with microorganisms. Such conditions include, but are not limited to, leukemia, diabetes, AIDS, IV drug abuse, and those requiring chronic corticosteroid therapy, genital actinomycosis. I was worried about that one.

[Laughter.]

CHAIRMAN EGLINTON: That's a little more exhaustive list than the IUD. Does that list sound like overkill?

DR. BLANCO: That sounds a little too much to me. I think the IUD's going to remain in place, and you've got some concerns from that. Here you go in, you do the procedure, and then the foreign object is out. I think we can gather some things from the IUD, but I guess I wouldn't want to be quite that exhaustive.

CHAIRMAN EGLINTON: When we were talking about it, we were talking more in terms of "at the time of the procedure, such as cervicitis, active herpes, upper genital tract infection." Does that cover it? Is that good enough without going to all of the other wording from the IUD?

DR. PERLMUTTER: I would say, "A patient with active upper genital tract infection, acute cervicitis or"--the wording that you had there--"or vaginitis, until treatment," whatever that wording is, and leave it at that.

CHAIRMAN EGLINTON: So it would be, "A patient with active genital infection"--

DR. PERLMUTTER: "Upper tract."

CHAIRMAN EGLINTON: --"at the time of the procedure, such as upper tract genital infection, untreated acute cervicitis or vaginitis, including bacterial vaginosis, until infection is controlled."

DR. BLANCO: That sounds reasonable.

CHAIRMAN EGLINTON: Is that okay? Okay. We'll keep this valuable reference here.

DR. PERLMUTTER: Well, wait a minute. Let me just bounce some ideas off. Are you going to talk about upper genital tract infection until it's controlled, or are you talking about vaginitis and cervicitis until it's controlled?

CHAIRMAN EGLINTON: That would be all inclusive, have the wording--

DR. PERLMUTTER: Well, the way you've just phrased it, it's all inclusive.

CHAIRMAN EGLINTON: Right. So we want to make sure that all active infections are treated before the procedure is conducted. Is that fair?

DR. MAPLES: Yes.

CHAIRMAN EGLINTON: Okay. Are we satisfied with the patient brochure?

MS. YOUNG: No, I don't feel like--I haven't had any reaction either from the panel or from the manufacturer about those two suggestions.

CHAIRMAN EGLINTON: I thought we wrote those. Don't we have the--we would include the new regulation, because there's that new regulation about the latex that has to go on everything. So that would cover the latex allergy, I thought.

The other suggestion was?

MS. YOUNG: Filling up the white space, with something about saying--just a little section saying what potential complications should I watch for after the procedure.

DR. MAPLES: Well, it does have a box about what

are the risks of ThermaChoice. That's not--

MS. YOUNG: No, I don't think that covers it. It's specifically telling the woman that, you know, if I get a high temperature, this is something that I should watch for because of the potential of infection.

DR. McCOLL: I certainly think we're very willing to put that in. I guess the recommendation I'd have is if you could give us the wording that you would like, we'd be very happy to put that wording in specifically. We're very willing to address that issue if that's what you'd like. We're not opposed to it by any means, I guess is what I'm saying.

DR. BLANCO: I think you would want to--let me add another one. I think fever's a good one. The other one might be pelvic pain because the concern would be with a perforation, and if there's any damage, for some reason the heat does come on when there's a perforation for some reason, one of the first symptoms would probably be pelvic pain and fever. So I'd say lower abdominal pain, fever, something about maybe excessive discharge, although trying to quantitate it in terms of more vaginal bleeding than a period--except for these patients, a period is a lot of bleeding. What others would you include?

MS. YOUNG: I was just thinking color of

discharge.

DR. BLANCO: Like bloody as opposed to more serous?

CHAIRMAN EGLINTON: I think that's getting too subjective. Abdominal pain, disturbance of bowel or bladder function. Because they're all going to have discharge, and, you know, serous, sanguinous discharge is just--that's to be expected. So I'm not sure what we're cautioning her to watch for.

MS. YOUNG: Well, I just think that, you know, normally before an infection, a high temperature is something that may develop.

CHAIRMAN EGLINTON: Oh, absolutely, fever. Right, fever, but I'm talking about the serious, sanguinous--I don't know how to characterize a discharge because they're all going to have a discharge, and we're not trying to get them all to call back, only those who are sick.

DR. PERLMUTTER: And a lot of them are having abdominal pain, so maybe abdominal pain not controlled by an NSAID or temp. over 100 degrees.

CHAIRMAN EGLINTON: We're trying to find the lady who has developed peritonitis or a perforation or has some other irritation, something like that.

DR. BLANCO: Also, abdominal pain after 48 hours

because they said most of the cramping with within the first 48 hours.

CHAIRMAN EGLINTON: Something that lasts beyond 48 hours, something that's getting worse.

DR. PERLMUTTER: What are we labeling this: "Reasons why you should call your doctor"?

DR. BLANCO: I think Diony said it. What was--

MS. YOUNG: I think that you should follow what I think is a good format where the patient herself is looking at this brochure and she's asking questions. So I just think that a question--so it should be phrased the same way, being what complications or what potential complications should I watch for.

DR. ZIPPIN: Or what trouble signs. My name is Norma Zippin with Gynecare, and we will certainly incorporate the suggestions that you have indicated. I think they're good ones. And in order to make it simple and have the women understand it, one way to say it is: What trouble signs should I look for after I arrive home or a few days after the procedure?

MS. YOUNG: Yes, fine.

DR. ZIPPIN: We'll think it through. And the ones that you mentioned, high temperature, odorous discharge, something like that, and the other ones that you have

mentioned are fine. And increasing pain, pelvic pain, we can include that as well.

CHAIRMAN EGLINTON: Any other comments on the patient brochure? Dr. Loffer, did we answer your--okay.

On Question 9, aside from any recommendations for the indications and contraindications, do you have any other suggestions for the labeling? I kind of hustled through this Question 4 since this is the labeling here, and what's made me think about it is some of the comments Dr. Shirk has made. And I'm sure I agree with everything he's said in this regard, but this says that this technique is a treatment for excessive uterine bleeding due to benign causes in women for whom childbearing is complete. But it doesn't say anything about--and it doesn't define excessive uterine bleeding. It doesn't define any evaluation.

I mean, the protocol is very clean. It only includes women who really clearly need this kind of procedure. But this statement doesn't really restrict the procedure to women who have something more than just they're tired of having periods.

DR. SHIRK: If you go to the physician handout here, there's a thing on pre-treatment preparation of the patient, but they don't include in that any of the recommended workup as to what criteria the patient should be

exposed to. I mean, basically, the question is: How should these patients be worked up? Do they just need a pelvic and an endometrial biopsy? That's certainly not acceptable for hysteroscopic endometrial ablation nor is it standard of care.

Basically, you know, the protocol for the study basically included either sonographic evaluation of the uterine cavity or hysteroscopic evaluation of the uterine cavity. So I think, you know, the uterine cavity certainly needs to be--you know, something needs to be put in there about that type of appropriate workup.

The other question I would have is basically all the data that we have on these patients is basically on pre-treated endometrium, and their statement in here says--suggests this, but it doesn't state that the patient needs to be treated. Basically, with the data that we have, do we have any data supporting that this is an effective procedure without pre-treatment or mechanical treatment of the endometrium?

Essentially what it's saying is you can choose to either do a pre-treatment or mechanical treatment, or you can choose not to do any treatment at all. It just suggests that you do this, and I guess what I'm trying to say is their effectiveness data--I mean, the data that they

presented is all based on basically the fact that they've used, you know, some--chosen a mechanical pre-treatment, but that we have no data regarding no pre-treatment of the endometrium.

CHAIRMAN EGLINTON: You're suggesting that this paragraph as a minimum has to say that the--has to describe what the studies have done thus far.

DR. SHIRK: Right. I think that it needs to state that basically, you know, some sort of thinning of the endometrial lining is recommended, and also that there should be recommendations for evaluation of the uterine cavity preoperatively. They're just assuming that anybody is using it understands the rules of the game. That's obviously not going to be true. If you have a nurse practitioner or a PA doing the procedure, then basically you're not going to have the same expertise. And there's certainly nothing preventing this from happening.

CHAIRMAN EGLINTON: We're back to my Dr. Yo-yo here again. I'm still troubled in this regard. This is a treatment for excessive uterine bleeding. Does it need to include excessive uterine bleeding not responsive to standard hormonal therapy or not responsive to something? Does there have to be a statement here that someone has made some reasonable attempt to control this uterine bleeding

using standard methodologies before resorting to this ablation? Or is this okay, that just anybody who self-defines subjectively that she has excessive uterine bleeding is a candidate for this procedure?

DR. SHIRK: Does that mean that everybody with fibroids is a candidate for doing this procedure before we treat the fibroids?

CHAIRMAN EGLINTON: Right. I think we need something more than just this in the indications.

DR. MAPLES: In part of your packet, you wrote that the--sent out the ACOG criteria set for endometrial ablation, and in the actions prior to procedure, it does say determine that the hormone treatment was not successful as part of the actions prior to procedure. Maybe we can adopt some of the ACOG endometrial ablation criteria. In addition, it says no finding of remedial cause by hysteroscopy, is on the endometrial ablation criteria.

DR. SHIRK: But then that sort of defeats the purpose of the balloon, that basically now you're condemning the procedure back to those individuals that can only do hysteroscopy. I mean, I think saline infusion and sonography probably is equal to--

DR. MAPLES: Okay.

DR. SHIRK: But, I mean, I think--

DR. MAPLES: You have to do some kind of evaluation.

DR. SHIRK: You've got to do some evaluation. I mean, some evaluation of the uterine cavity, including an endometrial biopsy, to rule out precancerous disease, and also you need to do something to rule out other existing pathologies that would not be covered. But I think it should be stated.

CHAIRMAN EGLINTON: Dr. Perlmutter:

DR. PERLMUTTER: Then that brings me back to the contraindications section, because, in fact, they didn't do anyone with a septate uterus and they didn't do anyone in which the uterine cavity was distorted by myomas. Therefore, that should be in the contraindications section since we have no information on that.

CHAIRMAN EGLINTON: Dr. McColl?

DR. McCOLL: I just want to point out, to reverberate that the contraindications section, if I understand correctly, is mainly geared for safety issues. We have listed in the precautions for the device--it says the safety and efficacy of this device has not been studied in patients with submucosal myomas, bicornuate or septate uteri, or previous endometrial resection ablation. I think we have addressed that.

As one follow-up, obviously the diagnosis, of course, of those would require some sort of methodology to do that.

CHAIRMAN EGLINTON: It's not stated in your brochure what those methodologies are, and I think it should be.

DR. McCOLL: I guess typically we haven't put in our labeling how to make physicians make diagnosis of things. We tend not to try to do that in our own labeling. Certainly we're open to listening to discussion about that, but we try not to get into the actual practice of how a physician does their actual diagnosis of their work.

DR. CHATMAN: It would be easy for somebody to interpret this to mean, though, excessive uterine bleeding due to benign causes in women, any filling defect could be treated. Any filling defect in the uterus could then be theoretically treated. So something should be said to eliminate those patients from being treated here.

DR. McCOLL: I'm just restating the precautions. I guess I would just go back and look at the precautions line. We have specifically addressed that in the precautions statement.

CHAIRMAN EGLINTON: What page is that on, Dr. McColl, the precautions?

DR. CHATMAN: It's on page 5.

DR. McCOLL: It's page--it's just below the warning. I have it as page 2 on mine. Hopefully we're looking at the same one. Unfortunately, my copy doesn't have the pages written at the bottom. It got cut at the copy site.

CHAIRMAN EGLINTON: Thank you. It's on page 5.

DR. McCOLL: It's immediately after the warnings section. It's warnings and then precautions.

CHAIRMAN EGLINTON: Dr. Shirk, do you think we should alter this statement of indications? It's very simple, just a few words, one sentence. Do you think that needs to be a more complicated sentence that includes something more specific than just excessive uterine bleeding, or is it okay just to have it describe in the next paragraph about treatment of excessive uterine bleeding and so forth in the manual?

DR. SHIRK: The only thing you could put in there is, you know, without demonstration of pathology. I mean, benign uterine bleeding without demonstrated pathology, which is what we're talking about, is that 200,000 people year that get hysterectomies without demonstrated uterine pathology because it's not applicable to fibroids or endometrial polyps or patients with other endometrial

abnormalities.

CHAIRMAN EGLINTON: So you would say it's a treatment for excessive uterine bleeding due to benign causes without demonstrated uterine causes?

DR. SHIRK: Right.

DR. MAPLES: Uterine pathology.

CHAIRMAN EGLINTON: Uterine pathology.

DR. SHIRK: Demonstrated uterine pathology.

DR. MAPLES: In premenopausal women.

CHAIRMAN EGLINTON: That stimulated a lot of comment. Dr. Spirtos is quickest to the microphone.

DR. SPIRTOS: I just have one question. I think that if you make that a broad label, the first thing that comes to my mind is adenomyosis. It's obviously pathology. It's a diagnosis of exclusion, and you couldn't exclude it.

DR. BLANCO: It's not demonstrable.

DR. SPIRTOS: Right, it's not demonstrable. But if you say only in a uterus without pathology, and if you're suspicious of adenomyosis, with a globular uterus or thickness of the myometrial wall--

DR. SHIRK: But we're saying demonstrated pathology. Okay? So, I mean, it's not demonstrable.

DR. SPIRTOS: So it's suspected.

DR. BLANCO: Well, I like the indication to be

simple. I like the simple sentence with the premenopausal, have it on here, and I think it may be--I think there does need to be a definition of what excessive bleeding is. I think that in the study it was very nicely done. It doesn't have to be that scientific. But whether it's the ACOG definition or some definition, I do think we need to define it. The appropriate place for that, and also to address the fibroids, might be to move the statements or leave them under precautions, but in the next heading, treatment of excessive uterine bleeding, where they talk about what it can cause, they can delineate what this study has not addressed on here, and it can also have a definition of what is excessive uterine bleeding that goes in from the indication.

DR. SHIRK: I think there are a lot of women who would probably agree and disagree as to what you define as excessive uterine bleeding over what we would medically agree or disagree.

DR. BLANCO: Well, I'm not giving you--I didn't know the definition. I just said we need to add it.

DR. SHIRK: So how do you define it?

DR. BLANCO: I was hoping you'd have that.

CHAIRMAN EGLINTON: Dr. McColl?

DR. McCOLL: I guess I can agree with the concept

of trying to keep the indications simple. What we've done in the way we've done the labeling was we followed it up with the treatment of excessive bleeding statement just following that, which states that patients should be evaluated to determine the cause of their excessive uterine bleeding before any treatment option is initiated.

DR. SHIRK: But I still think you need to define that the uterine cavity needs to be evaluated, and so I guess what I'm driving at is I think we need to put somewhere in there, as far as pre-op workup, whether we're doing it in the way that we change this statement of indications or that we put something in the pre-op evaluation situation there, you know, that we achieve the goal. My choice would be to leave the pre-op indications where they are, but basically state, you know, in this pre-treatment thing that either hysteroscopy or saline infusion sonography is recommended. I mean, that's--I mean, I know you don't want to dictate how somebody's treating it, but that's the only two ways you're going to adequately--with endometrial biopsy, adequately evaluate the uterine cavity. I think it needs to be stated somewhere in your literature that that's what needs to be done.

DR. McCOLL: It's possible we could--this might be a suggestion for you, is that in the section following

indications--and we've made the statement that patients should always be evaluated to determine the cause of their excessive uterine bleeding before any treatment option is initiated, you know, which may include hysteroscopy or saline infusion, ultrasonography or something.

DR. SHIRK: Should include.

DR. McCOLL: Should include.

DR. BLANCO: Well, no, I'm not going to agree with that, because I think--with the "should include," because I think then it defeats the whole purpose of this particular instrument. You know, okay, it may not work for submucous fibroid, but what have you done and how many people might it help. And does everybody have to have a hysteroscopy or a saline ultrasound before they get anything done? I mean, this essentially limits it again to whatever--somebody quoted 10 percent, or whatever, center where things can be done, and I don't think that that's what I would like to see. I think basically the whole point of this is to offer an alternative to women that doesn't have to go through all these other heavy procedures before you can do something with their menorrhagia.

I very much would like to see--and I'll just be very plain. I also wouldn't want to see this used inappropriately in patients who for just cosmetic reasons

are tired of having their periods and so they go in and have it. So I am interested in having a very clear definition that they have to be bleeding excessively, but I wouldn't want to limit it to purely having to have fairly sophisticated things before it can be used. I don't know that I can do it.

There are other ways, and you can look for fibroids, and you can look for some of these things. It doesn't have to be that they have to have this before you can use this instrument.

DR. SHIRK: The bottom line is saline infusion sonography is about as simple a procedure as you want to do. It doesn't take a rocket scientist to do a saline infusion sonography. If you're going to thread this balloon in, there's no trick to thread a pediatric catheter into the uterine cavity. I mean, it is--you know, I think that still, I think the criteria still is that we need some evaluation of the uterine cavity. I don't know how else to achieve it. I mean, if you can do the endometrial biopsy, you can do a saline infusion sonography. It's not that big a procedure.

If the patient ordering--I mean, you can also order it; certainly radiologists can easily do a saline infusion sonography. I don't see it as that big a test.

CHAIRMAN EGLINTON: Dr. Grainger?

DR. GRAINGER: That presumes, of course, that you have a $40,000 ultrasound machine in your office, and I just don't believe that general gynecologists have that equipment readily available to them.

CHAIRMAN EGLINTON: No, but the patient's managed care company has a contract with a radiology group in the periphery somewhere. They can do it.

DR. GRAINGER: But the other concern that I have about this discussion, these are really practice guidelines that we're talking about, and I don't believe that--you know, maybe I just have more confidence in my fellow gynecologists nationwide than I get the feeling of here, but I believe that gynecologists in general can make--can exclude malignancy, pre-malignancy, and as stated in the precautions, fibroids. Now, whether they choose to do that with--and I would say most of these patients have had an ultrasound examination of some kind, not necessarily saline hysterogram.

DR. SHIRK: But it's not going to be gynecologists that are doing it. It's going to be family practitioners and PAs that are going to be doing it. I mean, this takes it out of the gynecologist's hands. There's no question that this procedure will take endometrial ablation out of

the gynecologist's hands and put it into the realm of the primary care physician and basically his scope of treatment, which includes the PAs and the nurse practitioners. So, I mean, I think you're--I mean, you have to understand who's going to be doing the procedure.

DR. BLANCO: Well, let me add something to that because what you said is not quite what the paper says. There's a difference. What you said is how to evaluate if they have myomas and not use it, and that's not what the paper--what the precautions say is that the safety and efficacy of the device has not been studied in patients with submucosal myomas, et cetera. So it doesn't say anywhere that they shouldn't use them or that they should evaluate whether those are present beforehand. So it's a little different from what you said.

CHAIRMAN EGLINTON: Well, if we expanded this sentence--if we added another sentence for indications, could we have two-sentence indications? If we had another sentence and we lift it from the next paragraph, treatment of excessive uterine bleeding, we lift the sentence that says, "Patients should always be evaluated to determine the cause of their excessive uterine bleeding before any treatment option is initiated," if we edited that just slightly and lifted it up, said "should be evaluated to

determine the cause of their excessive uterine bleeding"--"Patient should always be evaluated to determine the cause of their excessive uterine bleeding and hormonal therapy, if appropriate, exhausted," or something like that, "before ablation is initiated." Something that indicates that there's something more than just the lady says, "I'm having too much bleeding." It requires some evaluation, without dictating practice guidelines, without saying what should be done, without saying exactly how she has to be treated, but indicating to the millions of primary care physicians and their physician extenders in their offices that something more than just the lady says she bleeds too much is necessary before you undertake this. Because everybody who practices medicine knows that Dr. Shirk is right. In the managed care revolution, that's exactly where this technique is going. It's going to the primary care office. And we have to protect the women from those who are less well educated than the average gynecologist. I agree with Dr. Grainger. The average gynecologist is not going to--is not as likely to misuse this because of ignorance, but a lot of primary care people are going to misuse it not because they're bad people but they're ignorant.

DR. SHIRK: I guess my question about putting some practice guidelines on there, how many times do you get a

Pap smear result back and it says recommend biopsy or recommend colposcopy. I mean, is this any different than putting something on a label like this that's basically to recommend? How is that different than the pathologist putting on a Pap smear report recommend colposcopy or recommend biopsy? Would you argue with the pathologist doing that?

DR. MAPLES: Yes. Sometimes I do.

DR. SHIRK: Well, obviously, directed at you, probably. But directed at a primary care physician, it's a whole different game.

CHAIRMAN EGLINTON: Dr. Perlmutter?

MS. YOUNG: Could we move on to other suggestions for labeling?

CHAIRMAN EGLINTON: Dr. Perlmutter may stab you with her ballpoint pen.

MS. YOUNG: I'm sorry. You're still on--

[Laughter.]

CHAIRMAN EGLINTON: I think it's time for a break, and we'll be back. We'll clear our brains and come back in 10 minutes.

[Recess.]

CHAIRMAN EGLINTON: Let's go ahead again, please.

Diony Young had some other comments on 9.

MS. YOUNG: First of all, when I was going through the labeling, I did notice quite a lot of typographical errors and so on, and I will bring one to your attention. On the post-treatment, 5.5, you're suggesting discarding the catheter and retaining the umbilical cord and disinfecting it for the next case. I think that's supposed to be cable.

I have two points that I wanted--one thing, Dr. Harvey earlier raised this issue, and I immediately--I had thought of the question already. How often can this procedure be used on one woman? And within what time period can it be reapplied? And it was mentioned in the international study that repeat ablations were done, and I just wondered if it was appropriate to include in the labeling something about reapplication of this particular procedure. That was one item.

The other was really a format one. On page 19, under the system labeling, you have in bold, "Do not autoclave." We're talking about cleaning sterilization now. And I just felt, as I was going through the labeling from beginning to end, that it would be more appropriate, because of the importance of cleaning and sterilization, it would be more appropriate to perhaps put that--and obviously you consider it important as well because you have it in bold on page 19, to put that section after post-treatment. I think

that would be a more suitable place to talk about cleaning.

Those were just the two things that I wanted to raise.

CHAIRMAN EGLINTON: Dr. McColl, do you have something to say about that?

DR. McCOLL: I'm just trying to get clarification. How we're phasing in our physician labeling on how to clean the device, is that what you're specifically speaking of?

MS. YOUNG: Yes, that information is given there, but I feel it's sort of lost. It's way toward the back of the labeling area under system, and I felt it should be further forward, closer to...

DR. MAPLES: Clean the unit? You're not touching the patient with it.

MS. YOUNG: Okay. I mean, I was just raising it as a possibility. I just felt that cleaning it in between patients was an important point that should be given earlier mention. That was all.

CHAIRMAN EGLINTON: I think it's in the section that begins on page 17 in our booklet, page 16, title "Maintenance." So, for continuity, I'm not sure that flows, moving it forward to the part about the patient. I understand your point, but it is in the back of the pamphlet, in the back of the manual under "Maintenance," and

probably is more cohesive if it's kept with all the other maintenance procedures, I would think. Do you think that it's satisfactory to leave it back there? It's maintenance of the equipment.

Dr. McColl?

DR. McCOLL: Just for a clarification, I think we actually have described that in a different part of the labeling which you might--if you look on page 5, much earlier, on page 5, under "Directions for Use," at 1.2 it says, "Disinfect umbilical cable as described at the end of this manual." So they could certainly reference back to that, and it has been brought to the very beginning of the document.

DR. PERLMUTTER: Dr. McColl, can you just describe to me what is disposable in this? It's the catheter plus that handle piece where the cable cords go on? The description here talks--

DR. McCOLL: Unfortunately, I don't have an overhead. I could get my slide out. That's probably the best way to do it. But--

DR. PERLMUTTER: Is this piece over here on page-- "Directions for Use."

DR. McCOLL: Yes.

DR. PERLMUTTER: Where the cables get attached.

DR. McCOLL: Right. It's actually--

DR. PERLMUTTER: Is that piece disposable where your control valve is?

DR. McCOLL: There's actually two--it looks like lines here or cables. One's actually what's called a pressure line, which is a tubing. It's a poly tubing, I think. And the other one is actually an electrical, reusable cable that connects the electrical components to the controller and to the device. So the electrical cable is disinfected and cleaned, and that's reused. The pressure line is actually part of the single-use device, which actually is connected.

DR. PERLMUTTER: And I guess what I'm asking you is you refer to the disposable catheter, but the catheter is more than just the catheter. It's also the piece that's got the cable entries in it?

DR. McCOLL: No, this--

DR. PERLMUTTER: You're shaking your head no, and you're shaking your head yes.

[Laughter.]

DR. McCOLL: When you use the word "cable," we use umbilical cable which has electrical wires inside of it. That's a cable. Okay? What is--

DR. PERLMUTTER: All right. The cable and the

pressure catheter, the pressure--

DR. McCOLL: Pressure line.

DR. PERLMUTTER: Pressure line.

DR. McCOLL: Is a tubing, pressure tubing.

DR. PERLMUTTER: Get plugged into a piece.

DR. McCOLL: Right, two different pieces next to each other. That's correct.

DR. PERLMUTTER: Two different pieces.

CHAIRMAN EGLINTON: If you look at your Diagram A, it has a balloon catheter. That's disposable. The balloon catheter originates from a controller handle. That's disposable.

DR. PERLMUTTER: Ah, that's what I wanted to--

CHAIRMAN EGLINTON: Is that true? Is that true?

DR. McCOLL: I'm just hoping I understood exactly what you said. The cable itself is reusable.

CHAIRMAN EGLINTON: No, forget the cable.

DR. McCOLL: Okay.

CHAIRMAN EGLINTON: Start from the balloon tip. The balloon and the catheter for the balloon are disposable; correct?

DR. PERLMUTTER: Is that all one unit with the handle there?

DR. McCOLL: Would it be helpful if I walk over

and explain it to you?

DR. PERLMUTTER: Yes, please. This up to here, is this all one piece?

DR. McCOLL: That's all one piece.

DR. PERLMUTTER: Including this?

DR. McCOLL: Including the tube that goes with the--all this is one piece right here, and the tubing is, in fact, connected that and comes with the package.

DR. PERLMUTTER: This is your--

DR. McCOLL: That's reusable. That's the only part--

DR. PERLMUTTER: Reusable. And this whole thing is changed with each patient?

DR. McCOLL: Yes.

DR. PERLMUTTER: Fine, thank you.

MS. YOUNG: Could I have an answer to the first question that I asked about how often can this procedure be repeated in a woman and how frequently?

CHAIRMAN EGLINTON: Does anyone have any feel for that?

DR. McCOLL: The answer is--how frequently can it be done? Is that the question you're asking?

MS. YOUNG: How often can it be used in one woman? And within what time period can it be reapplied in the same

woman?

DR. McCOLL: The answer is this is a single-time treatment, much like endometrial ablation. It's a one-time treatment that's used.

MS. YOUNG: I understand that, but also I understand that it was--in the international study it talked about repeat ablations using this technology.

DR. McCOLL: The answer is, much like endometrial ablation, there have been cases internationally performed where the device has been applied on a patient a second--original failure and applied to a patient with good success afterwards. But we have not done that at all in the United States study. None of the IDE study covered that at all. So we have not addressed that since we don't have the data from the PMA study to make comment on that.

So the answer is it has been done. It has been done in our international studies, but it has not been done in the PMA study, and that's why it was not addressed here.

MS. YOUNG: Well, you see, I wondered whether this should be mentioned in the labeling, because, in fact, if it hasn't been done here, then you wouldn't be recommending that, in fact, it be done because you don't have the data to say what the results would be. And so, therefore, don't you think that gynecologists or clinicians who are going to use

this should know whether or not--say they had a failure in Mrs. S and six months later they might think, well, you know, I'll try it again; it didn't work the first time, I'll try it again?

MS. DOMECUS: Can't the data from the international study be used to at least suggest some language?

DR. McCOLL: I'm not sure how you might want to have that language suggest it. Do you have a recommendation on what you're requesting?

MS. YOUNG: Well, we could probably come up with some. I mean, I just sort of threw it out because it was a question that came to my mind as I was going through the material, and as I say, I think the clinicians should be given some direction as to whether they should or should not repeat this within 4 months or 6 months or 2 years or not at all.

DR. BLANCO: Well, depending on how you wanted to say it, you could say there is limited data to support the--I guess "reuse" might confuse the issue, but--a repeat procedure, there's limited data to support the performance of repeating the procedure on the same patient who failed. Something to that effect.

DR. PERLMUTTER: Does that belong in labeling, or

is that something that we do by reading the literature?

CHAIRMAN EGLINTON: Or is that in training?

DR. PERLMUTTER: Or in training. Does that really belong in labeling?

CHAIRMAN EGLINTON: It's a negative statement. There are no data. There are lots of things on which there are no data. I don't know if we need to include something that has no data.

DR. BLANCO: I guess the concern is, would the panel like to see--and I'm going with what Diony was saying. Would they like to see, if somebody fails, the ability for the physicians to use this 6 months later on the same patient? Or would we like some statement that says since we don't know if it's effective, we should make--maybe the statement should be stronger. Maybe the statement is this is a one--you know, this procedure should only be utilized once on a patient until more data on repeated utilization is gathered. If you want a positive statement, you can do it that way.

CHAIRMAN EGLINTON: What do you think, Dr. Shirk?

DR. SHIRK: Again, I think that there's good data in the literature which suggests that repeat ablation hysteroscopically is of benefit. And I think at this point we don't have any data, but there's no data to suggest that

we shouldn't do it either. I think it's a point probably that--you know, just leave open-ended, don't address at all.

CHAIRMAN EGLINTON: Just leave it to clinicians' discretion.

DR. SHIRK: Discretion, right.

CHAIRMAN EGLINTON: Dr. McColl?

DR. McCOLL: Just as a comment here, we have listed in the precautions that safety and efficacy of this device has not been...in previous endometrial resection ablation. I mean, whether it's by balloon or whether it's by any other type of ablation, we haven't made a comment. We just don't have the data yet really to support--enough data. We have small numbers, but I think it's too early to make commitments.

DR. MAPLES: I agree with that.

CHAIRMAN EGLINTON: Diony, the clinicians aren't troubled as much by that. Is that acceptable?

MS. YOUNG: I'll trust the clinicians.

CHAIRMAN EGLINTON: Dr. Harvey is prompting me here. There were some additional points that were just listed here. Is there anything further on cervical cancer or Pap smear issues that we need to include? We talked about cervical cancer. We talked about endometrial hyperplasia. Is there anything else that anybody wants to

say about cervical cancer or Pap smear issues? Abnormal Pap smear preclude this? Please don't say that. I sat through an interminable FDA session on abnormal Pap smears earlier this year.

No enthusiasm for that? Dr. McColl, don't ask a question that's going to cause more discussion.

[Laughter.]

DR. McCOLL: It's only data.

CHAIRMAN EGLINTON: Okay. Dr. McColl, go ahead.

DR. McCOLL: During the lunchtime you asked us to try to put together some very quick numbers on our uterine lengths and things, and I have to say thank you to Dr. Downs because we did present the wrong data trying to put that together very quickly at lunchtime on those small numbers. We have had a chance since that time because the full log did appear within the last few minutes, and we were able to track those numbers down. So these are the UBT results from the one-year patients. That equals 108, and broken down by--it goes back to the number of saying why was our success rate for that group 94 percent. These were the exact numbers. We had understated the results for our results. There were a significantly more number of failures in the group than we were aware of. So here is the numbers on the one-year data.

In fact, what it says is that the results are actually very good in these shorter-length uteri. You can see at the bottom, the 16 of 17 is the 94 percent. I thank Dr. Downs for correcting us on our bad data. It made us look pretty bad, I think. Made ourselves look bad.

DR. BLANCO: Can you leave that up there for a second longer, please?

Thank you.

DR. PERLMUTTER: But you don't have the three cases of 4 centimeters there.

DR. PENDLEY: Laura Pendley, manager of clinical affairs at Gynecare. Unfortunately, we were scrambling in the back from a number of listings and got a couple of listings confused. If you can remember back earlier this morning, we had a number--when we talked about patient accountability, we started with 275 patients randomized into the study. A number of those got treated; a number of those were available at follow-up at six months and then now finally 108 at one year in the preliminary results.

This morning when we were talking about the 4 centimeter length uteri, those came from a listing of the 275 patients, the intent-to-treat group. So from that group, you know, we don't have one-year data available for all the patients. So just by chance, the 4 centimeter

uterus--the lady with the 4 centimeter uterus either is not eligible for one-year follow-up or is part of the 15 percent that hasn't come in yet from the preliminary data.

In fact, actually, I do know from one of my listings that one lady, one UBT lady with a 4 centimeter length uterus at 6 months was a success.

DR. McCOLL: Just to clarify, our confusion was over looking at our own listings between the intent-to-treat groups with FDA has recommended all patients that were entered into the study. So if the patient never got to treatment, we would consider those failures. That's where all those failures came from early on. Some of those patients were never treated.

DR. BLANCO: Let me ask the statisticians on the panel, as you would expect from a normal distribution of the collection of the patients, the patients trail off as you get into the lower uterine lengths, so that there's only three below 7 centimeters. But the study was designed to incorporate all the others.

Can you all address the issue of this tail? I mean, should you cut off 95 percent confidence interval? Is there any value, any reason for doing that? Or if you decided on--on entry into the study you decided on a range, then you stick to that, and you anticipate that if your

population is normally distributed, at the ends of your range you're likely to see a tail-off, and how do you deal with that? Do you understand what I'm saying? Over here, one of you two guys?

DR. DOWNS: It's not clear to me. You're concerned that the numbers are small?

DR. BLANCO: Well, I'm concerned--I'm going back to the issue of the numbers in the small--in the far end of the range--

DR. DOWNS: Then you wonder if that's sufficient for you to say it's okay?

DR. BLANCO: Right. Having entered into the study where this was the range and having--not surprisingly, when you see one end of the range, having few patients be on one extreme while most of these patients would be more in the middle. So does that clarify my question for you a little bit? It goes back again to--I don't want to salami-slice their data, but I also don't want to--you know, would like to not vote to let this loose down to 4 centimeters if we really don't have sufficient data to say something.

DR. DOWNS: This looks a lot better than the previous set of data, so it's a little easier that way. And what can I say? You can just say the data are limited in the lower ranges.

DR. SHIRK: Again, we only have data here down to 6 centimeters, so we've only dropped it a centimeter. We have not dropped it down to 4. So, I mean, you have no data on 4 and 5 centimeters. So I guess they can argue about dropping it to 6, but below there we have no data.

DR. BLANCO: Solved that problem? Okay.

MS. DOMECUS: Just to clarify, we're talking about as only a precaution statement saying that there's no data. We're not talking about limiting the indications statement. Is that correct?

VOICES: Yes, right.

CHAIRMAN EGLINTON: Have we covered all this? We talked about the time display. Nobody here understands why the time doesn't display the time of the procedure. That's troublesome. What would be required to make the time display display the actual active therapy time? Dr. McColl?

DR. McCOLL: That would probably take a complete reworking of some of the software, I would imagine, and I guess my comment goes back to the original comment that, you know, how important is it to know exactly how much was treated at 87 degrees if they were at 84 degrees for some of that pre-treatment time or not? Here, again, I go back to this, is this a safety issue you're concerned about? The maximum that the them could be is 12 minutes at this point,

as we mentioned to your comment earlier before. There is an audible beep in the treatment that immediately notifies the physician of when the time for treatment does start. So someone certainly can subtract back out, and that's, in fact, what we did throughout our study to determine how long the exact treatment time of 87 minutes [sic] was included because we did record pre-treatment times in our studies.

I guess my answer, from a company standpoint, it's a pretty significant change to a device, and I would certainly want to make sure that there's some rationale for it.

CHAIRMAN EGLINTON: Dr. Perlmutter?

DR. PERLMUTTER: I'm just thinking of documentation issues and putting down that it took X number of seconds--you say the average is 45 seconds--documenting in my record that it took 45 seconds to heat the device and we treated then for the full 8 minutes.

DR. McCOLL: I could clarify that very easily. At the end of the treatment, it says 8 minutes and 45 seconds on the controller. That's an 8-minute treatment, and that's a 45-second therapy. It would be very easy to document that without a problem, I think.

CHAIRMAN EGLINTON: Does that time stay on the digital readout?

DR. McCOLL: Yes.

CHAIRMAN EGLINTON: And so the power shuts down, or the heat shuts down, and 8 minutes and 45 seconds is left on the digital readout?

DR. McCOLL: Right, and we would record those, in fact, in the study on each individual patient so we had a sense of how long different pre-treatment times--pre-treatment therapy times were, the warming-up periods.

CHAIRMAN EGLINTON: And there's enough fail-safe in the system that it just cannot go on for more than 12 minutes? I mean, it unplugs itself from the wall or something, it just can't happen?

DR. McCOLL: Yes.

[Laughter.]

CHAIRMAN EGLINTON: Having been a user of Microsoft Windows Version 1.0, 2.0, 2.1, et cetera, et cetera, I'm always a little bit shaky on software.

Dr. Harvey, are we okay with this other list? Okay.

So were we to be involved in post--okay, training. We have to talk about training. Based on your review of the efficacy and safety, do you feel that a training program is necessary to instruct in the use of UBT? If so, is Gynecare's proposed physician training program adequate to

address user-specific safety and effectiveness concerns?

I'd like to suggest that the training is inadequate unless the practitioner is supervised doing the procedure, has to see one and do one under supervision, arbitrarily. Any discussion? Dr. McColl?

DR. McCOLL: Could I have you clarify how you would like that stated again?

CHAIRMAN EGLINTON: As a part of the training, to complete the training, the provider has to see the procedure performed properly and has to perform the procedure properly under supervision.

DR. McCOLL: This sounds like it's credentialing that we're talking about here, and I'm not--is that what you're discussing at this point?

CHAIRMAN EGLINTON: Hard to say. I don't know. How was it done with Norplant? Something similar to that.

DR. PERLMUTTER: Norplant, we actually got hands-on training. Anybody who got the device had hands-on training, because I was one of the trainers.

CHAIRMAN EGLINTON: Right. That's what I'm talking about, something like that. And I don't know how that was handled. Maybe it is--

DR. PERLMUTTER: But I'm not sure this is the same as Norplant, and I'd like to hear from the physicians that

did this as to how much training you think--I mean, just from the little that I see this, I don't see this too much different than some of the stuff I'm already doing. I'd be more concerned about loading--not loading the balloon, but getting the air bubbles out of the balloon with that 2 cc initially more than the actual procedure itself. So let me hear from you as to how much training you think we need.

DR. SPIRTOS: From my own personal experience, I had the training of having the controller and the balloon therapy explained to me and demonstrated on a model, that is, a plastic model. I then went through the procedure myself in terms of priming the balloon, inserting it, blowing it up, having it all explained to me.

The first time I faced my first patient in the operating room, I did the procedure. I didn't have the luxury of seeing someone else do it. And it was extremely easy. I remembered what I had learned. I reviewed all of the user information before. I had a nurse there to assist me. I did it. We went right through it, and this was a patient with a paracervical block and no other anesthesia because that's what she wanted done.

It's very user-friendly. I'm not sure that you would gain a lot by watching somebody insert it and stand there for 8 minutes, waiting for it to heat up, and then

watch them deflate it. Just like doing a suction and curettage, it's only when the residents actually do the suction that they get a feel for the inside of the uterus and they know whether they're at the top and they know whether they've got it positioned correctly. No matter how many times I tell them, they still have to learn it on their own.

So I think that the type of training that I had in terms of the background information on the evaluation of menorrhagia, going over the basics of the controller and equipment, how to assemble it, how to turn it on, how to prime it, how it heats, learning about the safety of it, and then using it with the assistance of a nurse who understands the machine, was really all that it would take.

DR. PERLMUTTER: What do you think about a good video to do this? Do you think it could be done with a video?

DR. SPIRTOS: Yes, and I believe that that is part of what the training program includes at one part of it.

CHAIRMAN EGLINTON: But, Tanya, I'm not talking about you. I'm talking about all the other people who are going to use this. There are a lot of other people who are going to use this, and some of those people have not done hysteroscopy, have not done a thousand D&C's. You know who

I'm talking about.

DR. SHIRK: Do you think a PA could do this that easily?

DR. SPIRTOS: I had an excellent nurse practitioner. Excellent. No, it depends. I mean, we can't micromanage what's going to be done in the community. All we can hope is that when we've got these devices that have a lot of usefulness to the population, that people are going to be evaluated properly and that the machine's going to be used properly and that we're going to get the effect and the safety that we are seeing here today.

I think there's a lot of skills in many things, whether it's putting in an IUD or putting in a Norplant or taking out a Norplant, there's always going to be people who are--physicians who are on the upper and lower part of the bell curve.

DR. BLANCO: Well, I think the problem, though, is that we do need to address the issue of who this is going to be put in by. And I agree with you. If you're trying to teach an OB-GYN who's done some D&C's and dilatation of the cervix, who've put in IUDs and has put things inside the uterine cavity, I think basically you need to teach this individual how you put the machine together, all your different techniques, and how you do it.

But if it's also going to be available for use by people who haven't had that kind of experience, I think that presents a different problem. I think you've got a lot of issues of perforation and a lot of issues that they might not be as familiar with in terms of putting things inside the uterus. I think somebody who's put in IUDs probably, you know, has a big leg up on this kind of procedure because they've been doing this kind of thing.

So I think the issue for me on what kind of training is needed depends on who's going to be putting these in. If it's going to be people who do intrauterine procedures all the time and put in IUDs and do this kind of thing, the level of training that's required of those probably has to do more with familiarity with the machine. If they're aimed at someone who's never put anything inside a uterus, then I think you need a lot more than what you've got on this report.

DR. SPIRTOS: Well, I don't think that this device is geared for people who haven't put anything inside the uterus. First of all, we're talking about the evaluation of excessive bleeding. We're talking about whether it's this year toy of sonography or next year's famous way of evaluating the endometrial cavity. It has to be evaluated. The patients have to be followed.

So the usual people who don't look at the uterus and don't put anything into the uterus are not going to be the people who are looking to use this device and follow their patients. So I think that it's--it will most likely be used in outpatient surgery centers to start with.

DR. BLANCO: The problem is, what I don't like is "the most likely." You know? I mean, that opens it up to a lot of folks. And while what you're saying is true, that doesn't say is it going to be physicians, is it going to be physicians who pass the patient off for this procedure to PAs or nurse practitioners, and what's their training going to be, and what kind of physician? That's my concern.

DR. STEEGE: John Steege. I can basically simply say ditto to the previous comments. I share your concerns about the practitioner who has never passed anything into the uterus. That person first needs to be trained how to take an endometrial biopsy before you do anything like this. I absolutely agree.

For those who have gone down that road and at least know what the feel of a sound is as it feels the uterine fundus, then this procedure--you know, it's not a no-brainer, but it's a small-brainer. Okay?

I do share your concern that if people have never before negotiated the cavity of the uterus that they should

learn this procedure in the same way that we would teach them how to do endometrial biopsies or any other intrauterine entry.

DR. BLANCO: Well, I totally agree with you, and that's the issue for me. I don't think you've got a one-size-fits-all situation here. I think you may need to tailor your education to who your audience is.

DR. CHATMAN: Who is the audience?

CHAIRMAN EGLINTON: Dr. Yin?

DR. YIN: I'd like to introduce Dr. Ben Schultz, and he would like to make a recommendation.

DR. SCHULTZ: I think one option for you--and I think the points that are being made here are extremely valid as to who is the audience and who are the people that are going to be doing this procedure. And if you notice, in the label on the first page, where it talks about caution, Federal law restricts this device to sale by or on the order of a physician, we have the option of expanding that and restricting this device, or any device, for that matter, to not only physicians but physicians who are trained or experienced in the use of a particular type of device and in the management of a particular type of condition.

Certainly, you know, based on your recommendations, we could certainly work with the company

and develop some wording there that would address some of those concerns, and that might make the issue of training a little bit easier for you.

CHAIRMAN EGLINTON: Dr. McColl?

DR. McCOLL: From the company's side, we certainly were--as I mentioned earlier, we're very interested in making sure the appropriate patients are selected for this procedure and, in fact, have put together a very comprehensive program to train our new users how to use this device. We've supplied that information to the FDA. Included there's a long list of the content of the training documents. That would be part of training package that we put into--I guess the emphasis I'm just trying to emphasize here is, as our clinicians have said, that the use of this device and the ability to use this device is not the issue we're talking about here because the device is generally very simple and easy to train someone how to use and the directions for use of the device.

What we're discussing here is the appropriate selections of patients, and that's what patient labeling is about. The labeling should list in it what are the appropriate patients to be using on this device, and it should be very clear and laid out, and that's what we've spent quite a bit of time here discussing.

My point is that we as a company are certainly very committed to training the individuals with the material that we've put together, very comprehensive material. What I'm very concerned about is getting into an area that's already controlled by hospitals and other areas, which is essentially credentialing, how to use a particular procedure by limiting the number of times the person has used the device before the device would be sold to that person.

I guess what I'm trying to understand here is we're walking into an area that's more into the practice of medicine than it is necessarily in the labeling of what are the appropriate patients to be selected for this procedure.

CHAIRMAN EGLINTON: Dr. Chatman?

DR. CHATMAN: I just want to repeat my question. Who is the audience Gynecare is targeting? Gynecologists? General practitioners? I mean, who--

DR. McCOLL: There's no question in our mind that the gynecologists are where this procedure belongs. That's what we've been--all along from a company standpoint, that's what we've been aiming at. Of course, people are going to--I'll stop it there, I guess, at this point. You can speculate all you want, but that's what we as a company are aiming at.

CHAIRMAN EGLINTON: Dr. Shirk, how do you feel

about training?

DR. SHIRK: Again, I guess the question of audience comes up. I agree that we can't get into the realm of credentialing. We talked earlier about getting into the realm of patient care, and so that I think that, again, the issue of credentialing is certainly probably not in our domain.

I think that certainly setting up adequate training programs is essential and that there needs to be some hands-on training in this situation, at least from a model standpoint if not, you know, a patient standpoint. But, you know, I don't know how we dictate that or what the rules are from the FDA standpoint about doing that.

CHAIRMAN EGLINTON: Can I ask the company, for the clinicians who did the study, did the studies, did the procedures, how was that set up for showing them how to use the equipment and doing the first procedure? Did everybody do it blind, as Dr. Spirtos did, so to speak? How did that work?

DR. LOFFER: I obviously needed a little more help. I had the opportunity to watch George Vilos do several cases in Canada, and then it was brought to my operating room. I knew the theory behind it and proceeded with doing it myself.

It's an incredibly simple procedure. I share with some of the concern that it will fall into the hands of people who don't do a good job in working up the patient. I also agree that you can't credential it. That's done on a local basis.

You know, the thought occurred to me, in reality-- and I'm not suggesting that the FDA should do anything but protect patients and not give business to the trial attorneys, but there is a fail-safe mechanism out there. You get the yo-yos that are going to blow it. They're going to get called on the carpet. That's not to the company's advantage, and I don't think they want it to go that way. I think they want to do it this way, and from my vantage point, I had less than this and didn't feel that I was undertrained.

CHAIRMAN EGLINTON: I think you can appreciate what we're all talking about here. If there start to appear major complications with this procedure, the provider's going to get sued; the surgical center is going to get sued; the company's going to get sued. And the question is going to be: What kind of training did you provide? What kind of training did you have, Doctor, before you did this procedure? And then we're kind of struggling with how do you address that to protect patients.

DR. BLANCO: Well, I think the issue--I mean, we're not getting into credentialing and any of that. I think the issue is--yes, I would agree, I'm sure it was easy for you. I've worked in the intrauterine environment. It would probably be pretty easy for me. But I think that I like the concept that there should be some statement that use of this device should be restricted to physicians who have some knowledge of intrauterine--let me think for a second. My mouth started before my brain kicked in here. But it should be restricted to physicians familiar with the introduction of surgical instruments into the intrauterine cavity. Because I agree. I think it's what you and I both said. For most folks who do D&Cs, who have put sounds in the uterus, this is not going to be much more than familiarizing yourself with how the controller works and the catheter and the feel of the catheter going in. But somebody who's never put a catheter inside a uterus, quite frankly, I don't think you guys want that person out there putting these things in because you're going to get the lawyers coming after you.

So I think a statement to the effect that--worded better than I've come up with, something that the use of this device should be restricted to physicians familiar with introducing surgical objects into the intrauterine cavity,

something to that effect, would actually be protected. Maybe you have that in there.

CHAIRMAN EGLINTON: Dr. Loffer?

DR. LOFFER: The first item under warnings, "Failure to heed any warnings or precautions could result in serious patient injury." Bullet 1: "Endometrial ablation procedures using the ThermaChoice UBT system should be performed only by medical professionals having adequate training and familiarity with the technique." That's the very first warning that we have in there.

DR. BLANCO: But that's not quite it because what happens if a family medicine or internal--I'm going to include everybody, okay?--comes to your seminar and goes through your process of training, which is putting one of these things inside a plastic uterus, and he says, "Hey, guys, I went to your training. I got trained."

You see, your wording would allow that to be an acceptable individual to do that and I would counter that that's not who you want. I mean, you want somebody who's put a few sounds into the uterus beforehand. Do you see what I'm saying?

DR. EGLINTON: Dr. Loffer, do you think that if a primary care physician or a nurse-practitioner has adequate training and experience to sound the uterus and do a

Pipelle, that person is fully capable of doing this, that this isn't any more complicated than that? They should be all right?

DR. LOFFER: It is certainly more complicated but not much more complicated. I'm not suggesting with that minimal training they ought to be doing it but it's very little more than that, in reality.

DR. McCOLL: McColl again. I just want to also emphasize that that warning, first of all, it was listed in a warning, obviously a very significant part of the labeling. In addition, it follows up by saying that we should consult the medical literature relative to various endometrial ablation techniques, indications, contraindications.

I think my point as a company, I think we're very sensitive to what's been mentioned here. For the success of this device and from a company's standpoint it's very important that the appropriate patients are treated. In the long term it's not good for the company to have the wrong individuals using this device and that's why we have put together extensive training programs. We believe making sure this device is in the adequate hands of the right person is very important to us as a company for the long-term success of any product, and bad publicity early on or

any time during a product's use can be devastating to the product itself.

So it's truly in the best interest of this company to make sure that this device is used in the right hands. I'm just concerned about getting into areas outside of where we have been already.

DR. EGLINTON: So is there any enthusiasm on the panel for going beyond the training program, as outlined by the company, for example, as I suggested, see one, do it? Is it okay just the way it is, the way the company has it listed?

DR. BLANCO: Well, no, I've got to create trouble. I still believe that it needs to be more specific. Whether they want to put a proviso in that people who enter their training program need to have some familiarity with how to introduce instrument into the uterus or whether they would like to do it as part of the warnings, I think it for medical-legal purposes and to allow them, for their benefit, it needs to be someplace that you need to have some familiarity with putting things inside the uterus before you ought to be doing things with this device.

DR. CHATMAN: I think I agree with Dr. Blanco. I think that in order to protect the women that we serve, in order to protect the FDA, in order to protect the company

and in order to let the lawyers starve a little bit we ought to be sure that the people who are trained have some information about how to go about assessing the uterine cavity, assessing the uterus and assessing the pelvis itself.

In addition, of course, this experience--I guess Dr. Loffer can speak to this better than anybody else here--the experience that the people in the UK had using the resection techniques and the original endometrial ablative techniques and the kinds of results that occurred when the general practitioners got hold of those instruments--I mean, we probably won't repeat that kind of thing here with this but I think it's potentially a disaster.

DR. BLANCO: But I don't think the issue is whether the general practitioner--I think anybody that gets appropriately trained could do this and the issue is what is appropriate training? It could be a nurse practitioner or a PA. It could be a family medicine doc, an internal medicine doc. If somebody knows their way inside the uterine cavity and they become familiar with this process, that's somebody who could be safe doing this.

So that's the issue we need to address. I'm not trying to limit, by specialty or credential anybody or do anything but I think the requirement is familiarity with

putting things inside the uterus. It's a blind procedure. You've got to know how far that sound goes. You go from there. I'm not trying to limit it to gyns or anybody else but I think that requirement has to be there.

DR. EGLINTON: Dr. Yin, do you think the FDA has enough words here that you can work on this with the company?

DR. YIN: Yes, I think we can. If any one of you would like to be on the committee, we will be more than glad to share the wording with you because we did require quite a few training program before. So this is absolutely not new to us. Usually we are very fair to all sides.

But first of all, what we need to do is to read over the training program one more time to see what's the true concern.

DR. EGLINTON: Dr. McColl?

DR. McCOLL: I guess just to address Dr. Blanco's question, I don't think we as a company would be opposed to amending the proposed labeling here to do what you've said, that familiarity with the technique of placing instruments inside the uterus. I think that's certainly a reasonable thing. We certainly wouldn't want people using this device until they are familiar with being inside the uterus and I don't think we, as a company, would be opposed to doing

that.

DR. EGLINTON: Okay. What we'll do here, and we're getting close to the end; at the end the bottom line is probably going to be that we will have a subcommittee of the panel, interested members who will work with the FDA on editing an agreement between the company and the FDA as we kind of flesh out some of these issues. All this is on tape. It'll embarrass all the rest of us for time immemorial. So this can be worked out with more editing.

DR. McCOLL: Can I just get confirmation from the panel that we're not talking about credentialing here but we're talking about labeling, which I think is really critical. I think we need direction to make sure that we're not talking about necessarily credentialing but we put it into the wording of the labeling document.

DR. BLANCO: I'm not interested in credentialing whatsoever but I can't believe that when they were putting the IUD together, in their training for new people who were going to put in an IUD, the only requirement was that they put it into one plastic uterus under supervision. I mean, I have to believe that somebody said you do that a couple of times and then the first one you do on a human, somebody's going to watch you or you're going to have some familiarity with what you're putting inside the uterus.

I guess that's what I'm saying. I'm not trying to credential anybody.

DR. CHATMAN: You can't credential anyway. Credentialing is done at the local level, the individual hospital level. So you can't even certify.

DR. BLANCO: What you said would be fine with me.

DR. SHIRK: The question would be basically if a physician calls you up and says I want to order four of these and he has no history with you as far as training, do you sell these to him or do you not? I mean, does he have the right to buy them or does he not have the right to buy them? Obviously credentialing in a private physician's office is out of everybody's hands.

That would be my only question and I guess probably maybe not even under your control. Do you have to sell to somebody who's not had any contact with your training programs?

DR. EGLINTON: Okay. We need to talk about post-market study. Under current FDA guidance, the patients are scheduled to be followed for a total of three years. We've already had about 85 percent of them that have come through one year. We've got two years post-market.

Is this plan adequate? Is this acceptable?

DR. BLANCO: I guess, since you're looking for

somebody to say something, I'll be the usual patsy. I think a total of three years follow-up on patients for this kind of thing would be sufficient. I think that's what they're talking about, and see whether there's any complications that haven't come to light. I think other than knowing a little bit more about how many of these folks will go back to bleeding, it doesn't sound like we'll probably get too much more else, but it would be worthwhile to know that you can counsel the patient about what's the rate.

DR. EGLINTON: Dr. Shirk?

DR. SHIRK: The question is obviously how long is long enough? There's certainly some data coming out of Canada and Great Britain that there's still a fall-off at five or six years, that there's still a significant fall-off. And it would certainly be, I guess, interesting to look at the procedure and its efficacy at those time frames.

Again, it comes down to a question of how long is too long? But certainly five years may be a more rational answer than three years.

MS. DOMECUS: I think the five years is probably an unreasonable burden to put on the manufacturer. And three years, it would be doing quite a good job to follow up these patients with a significant retention percentage to address the long-term issues.

DR. YIN: May I propose something?

DR. EGLINTON: Dr. Yin.

DR. YIN: I'd suggest that we will follow the three years and when the three years is up we will look at the data and then reevaluate if we need to continue our monitoring. Would that make sense to all of you?

DR. EGLINTON: Any other comment?

DR. YIN: I have a question for Dr. Shirk. In your review, under labeling, you did ask a question. Was that addressed, on page 5 of your review, under labeling? Did we address that question for you already?

DR. SHIRK: I guess my question was basically in the information to the physician is basically a question about debugging the equipment in the operating room. If you undergo a failure or the machine shuts down during the procedure, what's an outline step of what the physician should do to figure out what went wrong, whether there was equipment failure, whether there was a perforation; if there was equipment failure, what things need to be looked at to find how to get the machine in an operable state? Because certainly most of our crews and most physicians are not going to have the technical ability to debug a problem.

DR. PENDLEY: Laura Pendley with Gynecare.

Of course, that's a pretty global question, to go

through all the scenarios that possibly could happen but let me answer just a few things.

Number one, there's a user's card under the device that just gives abbreviated instructions of use. Of course, that's not instead of the package insert and instruction manual and video and everything else but it is there as a reminder.

Secondly, the device itself, in the whole realm of alerts and hazards and so forth, there are visual prompts on the controller that leads the operator through some troubleshooting steps or just stops the procedure altogether.

In terms of you did mention one particular case of uterine perforation or possible uterine perforation, in that scenario treatment pressure of 160 millimeters of pressure would not be reached with the maximum volume of 30 cc's. And in that instance, the operator has already been instructed to withdraw the catheter, the fluid, and check for either A, a balloon leakage or B, a uterine perforation.

Does that answer your question?

DR. EGLINTON: What happens if somebody pushes the button for "go" before the balloon has been inserted?

DR. PENDLEY: You wouldn't have adequate pressure for the heater to activate itself.

DR. EGLINTON: Or before it's fully inserted. Do you push "off" and start over?

DR. PENDLEY: Nothing would happen.

DR. EGLINTON: But now you're in the operating room, you're scrubbed. The balloon is hanging down between your legs; it's fully inflated. What do you do now? The patient is asleep. What do you do now?

DR. PENDLEY: Again if you have the balloon with whatever volume in it but it's not within the uterine cavity, you're not going to be under pressure. The balloon itself, against atmosphere, won't--

DR. EGLINTON: Right, but now you're eating up anesthesia time. What do you do? How do you proceed and do your procedure?

DR. PENDLEY: You would withdraw the fluid and at that point it would be a primed catheter. Go ahead and insert it into the uterus and proceed.

DR. EGLINTON: But the machine is already--the button's already been pushed for "go." Is there a reset? See, we're talking about real-life scenarios. If it's possible to screw it up in the operating room, it's going to be screwed up. That's what Dr. Shirk is talking about.

DR. PENDLEY: Nothing would happen.

DR. EGLINTON: What do you do to start over?

DR. PENDLEY: There would be no need to reset at that point. It wouldn't activate the heater; nor would it de-activate your ability--

DR. EGLINTON: It doesn't start the timer if the pressure isn't--

DR. PENDLEY: No, that's correct.

DR. EGLINTON: So nothing happens if you push "go" and it's not appropriate to go?

DR. PENDLEY: At that point the prompts are telling you to go through the priming process.

DR. SHIRK: What I'm saying is it would be nice to have a little sheet for the OR that goes through all this. I mean, you described to me several--two or three different things that, partly in the machine and partly underneath the machine and basically there ought to be some kind of a user's thing that basically tells the user, you know, all the steps that they should go through, even if the machine is prompting them to do things. I mean, anybody who's worked in an OR knows that things that are obvious don't become obvious to a lot of the people.

DR. EGLINTON: Dr. McColl?

DR. McCOLL: I think we fully appreciate, Dr. Shirk, your concerns and we have been trying to work as many of our users at this time to improve the usability of the

device, including small cue cards, those that are taped on top of the box, error-code little cards. We've been doing all sorts of things that would directly address these and we would be very open to any other recommendations you might have that would make it easier.

The best input typically comes from the people that have been using the device routinely because those are the ones that can give you the best direction on what's really necessary.

DR. SHIRK: Yes, but it's the people that get it in the OR and basically haven't been using it routinely, it's new to them, or that you keep changing OR crews every time you do the procedure so that you never see the same OR crew; the nurses are not used to the equipment, have no familiarity with the equipment. You're making an assumption that once a crew figures out what's going on, but what if you don't get the same crew all the time? I mean, there's a lot of places that obviously if you see the same people on two procedures, you're lucky.

So what I'm trying to say is that all of us are saying basically to put together some kind of a flow sheet that goes with this thing that's on the machine, on the box, that basically outlines a debugging process.

DR. McCOLL: And we're in full agreement with you.

DR. EGLINTON: Are there any other issues of safety or effectiveness, item 12?

DR. BLANCO: Did any response ever come of the bubble issue? Remember you asked about bubbles, if there were any bubbles, way earlier in the morning? Did they ever--

DR. NEUMANN: I think I asked about that and I think the FDA is going to look into it.

DR. BLANCO: Okay.

DR. EGLINTON: Okay. And we were past another contraindication that I don't think we've discussed earlier, which would be an IUD in situ. Does that cause any heartburn just to list that, to add that as a contraindication, IUD in situ?

DR. PERLMUTTER: I'm particularly concerned about the IUDs with copper. I work in a Chinese community health center where we still see stainless steel IUDs and I can think of people using this without taking them out.

DR. EGLINTON: All right. We seem to have reached the bottom of our list of discussion questions. Dr. Perlmutter, did you have anything to offer, perhaps something that you had offered earlier in the day and then withdrew?

DR. PERLMUTTER: I would like to propose a motion

that we approve this with modifications, as we've already outlined them.

DR. BLANCO: Second.

DR. PERLMUTTER: Do we have to list each one?

DR. EGLINTON: I don't think we're capable of listing them. I mean, they're on film.

DR. PERLMUTTER: Well, can we do this with modifications of the patient brochure?

DR. EGLINTON: Mr. Pollard comes to the podium to rescue us from this quagmire.

MR. POLLARD: I was going to offer you some suggestions for listing the conditions without going into graphic detail. As I heard it, and the panel will have to correct me if I'm wrong, there were modifications to the patient labeling, there were modifications to the professional labeling and, as Dr. Yin pointed out, we're going to make a small group of the panel work with us--I mean ask a small group of the panel to work with us to deal with the company, to make those fixes. We would obviously use the transcripts, as well as our notes, to do that.

There is the issue of the remaining 15 percent of the patients to add to the one-year follow-up data. And there was the issue of the two-year follow-up in the post-market setting. Those were the four issues that the panel

discussed.

Mr. Murray brought up one residual software question that we felt we could work with the company to resolve. And there was the question of the air bubble issue that we agreed that FDA would work with the firm on.

So those are six conditions.

DR. PERLMUTTER: I've got five. What was the sixth? I've got patient labeling, the physician labeling, including developing a subgroup, the follow-up data, the two-year follow-up--

MR. POLLARD: The software issue.

DR. PERLMUTTER: The software, okay, and the air bubble.

MS. DOMECUS: What's the two-year follow-up issue?

MR. POLLARD: We have one year follow-up data within the PMA before approval and the company would agree to follow those same patients an additional two years post-market.

DR. PERLMUTTER: And we have the 85 percent in that 15 percent that we need to follow up on. There were two follow-up issues.

MS. DOMECUS: I'm not sure where we left the indications statement, though. Did we finalize how that's supposed to be worded?

DR. EGLINTON: That was part of the physician, the professional labeling, to expand that statement slightly.

DR. YIN: Just to add the word pre--

MS. DOMECUS: Premenopausal, yes, but I think there was some discussion about excessive uterine bleeding and I'm not sure we left that.

DR. EGLINTON: Right, without getting into credentialing, without getting into listing of the work-up but just a slight expansion of that.

DR. PERLMUTTER: I'll see if I can do this. I would like to propose a motion that we approve this PMA with the following modifications--under the following conditions, that the patient labeling be reworked, that the physician labeling be reworked, including developing a panel to work with the FDA and the company to do the labeling changes, that we get further follow-up data from the 85 percent of the 100 percent of the women at the one-year follow-up, that we do complete two-year follow-up, that we resolve the issue of air bubbles within the system and that we resolve the software issues.

DR. EGLINTON: Is there a second?

DR. SHIRK: Second.

DR. EGLINTON: Any discussion?

Okay, those in favor of the motion as stated,

raise your hands.

Opposed voting members?

So the motion carries.

DR. PERLMUTTER: We have an abstention.

DR. EGLINTON: Oh, Dr. Chatman is a voting member. Sorry, one abstention, sorry.

Now we survey each of the members, beginning with Dr. Blanco, as to why you voted the way you did.

DR. BLANCO: I voted in favor because I think they provided sufficient evidence to show safety and efficacy. I voted for the conditions because I think it needs to be clarified as to which women this should be utilized on and how it should be processed and what physicians should be-- what training is required to use the device and that they needed to meet some of the conditions.

DR. EGLINTON: Dr. Chatman?

DR. CHATMAN: I abstained because I'm not quite sure that we listed all the conditions that we've discussed today that need to be reviewed before the final approval is given to the device. I'm satisfied that the device is safe and efficacious but there are some conditions that I think we have not outlined.

DR. EGLINTON: Dr. Shirk?

DR. SHIRK: I voted for it because I believe in

endometrial ablation as a procedure. I think they've demonstrated that it is safe and effective. I think there are some significant questions still related to the labeling and end use situations but in general, I think that the device will prove to be a benefit to most women in this country.

DR. DOWNS: I voted for the device because I thought it was safe and effective and I want to add that I especially liked the way this study was designed and executed. I thought the write-up was clear and straightforward.

DR. PERLMUTTER: I voted for this proposal because I do because that this device is safe and effective. The modifications are there because I feel that it's important that we have proper labeling and that this be fine-tuned. And I must agree with Dr. Downs that this is one of the nicest protocols that I have ever read and I did serve on this panel before. So it was a pleasure to read it and I want to thank the company.

DR. EGLINTON: Dr. Neumann?

DR. NEUMANN: I'm not going to repeat myself but yes to everything that was said before. I think one additional comment is that it appears as though the company is more than cooperative and willing to work with the FDA in

terms of working out these conditions and I just encourage both sides to hurry up and get it done.

DR. EGLINTON: Thank you. I would like to echo the congratulations to the sponsor. I think you've done a very nice job in putting this study together, designing it, working with the FDA, working through it and presenting it, especially. Thank you very much for a very professional presentation.

I'd like to thank the FDA reviewers, as well. This was almost my last meeting. I have one more. I've been here for nine years now and I think the FDA presentations get better every meeting and it really makes the work of the panel much easier.

Dr. Yin?

DR. YIN: I have two questions. One is for Dr. Chatman. Can you list the part that's missing so we don't feel like we have failed you?

DR. CHATMAN: I wish I could. Some of the items in labeling are a major concern to me, that we have not specified as a condition of approval that I think we need to spell out.

In addition, there were other conditions that we did not--and I think Dr. Perlmutter's motion sort of came real fast and probably might have missed some things that we

discussed during the day. I'm not sure.

DR. YIN: Okay. And the second thing is should you suggest the panel members to us?

DR. EGLINTON: I was going to ask if Dr. Chatman could work, and just to make sure that we get your input, to do the things that we need?

DR. CHATMAN: If I change my vote, would--

[Laughter.]

DR. YIN: Too late.

DR. EGLINTON: As well as Dr. Perlmutter almost volunteered.

DR. PERLMUTTER: I think I got volunteered.

DR. EGLINTON: Dr. Shirk, could you help, as well?

DR. SHIRK: Yes.

DR. EGLINTON: And we'd really like to have Diony Young participate, as well, to make sure we have the patient brochure tightened up.

Anyone else who'd like to participate, as well, to help make sure this gets smoothed out?

DR. YIN: Just remember, we expect response the next day.

DR. EGLINTON: Mr. Pollard?

MR. POLLARD: I just wanted to assure Dr. Chatman there were an awful lot of comments about the labeling and I

think when Dr. Perlmutter was saying subject to making changes to the labeling, the professional labeling and the patient labeling, we intended to carefully go over the transcripts and the notes of the people involved here to make sure we covered all those aspects, and we'll do that with you.

DR. YIN: I have the last say. I do want to thank the panel very, very much and especially Dr. Eglinton. And when he says "yo-yo," he does not mean that. That's his endearment type of addressing it. If he really doesn't like you, he will not call you "yo-yo." So we've been called "yo-yo" many times. We know he likes us because he's been here with us for nine years. So remember, that's his endearment note.

And I do want to thank the company for doing a very good job, also.

Thank you, and especially my own reviewers. They have done me wonders again. Thank you.

MS. ELISA HARVEY: We can adjourn the meeting. The panel will reconvene tomorrow at 8:30.

[Whereupon, at 4:35 p.m., the meeting was adjourned.]